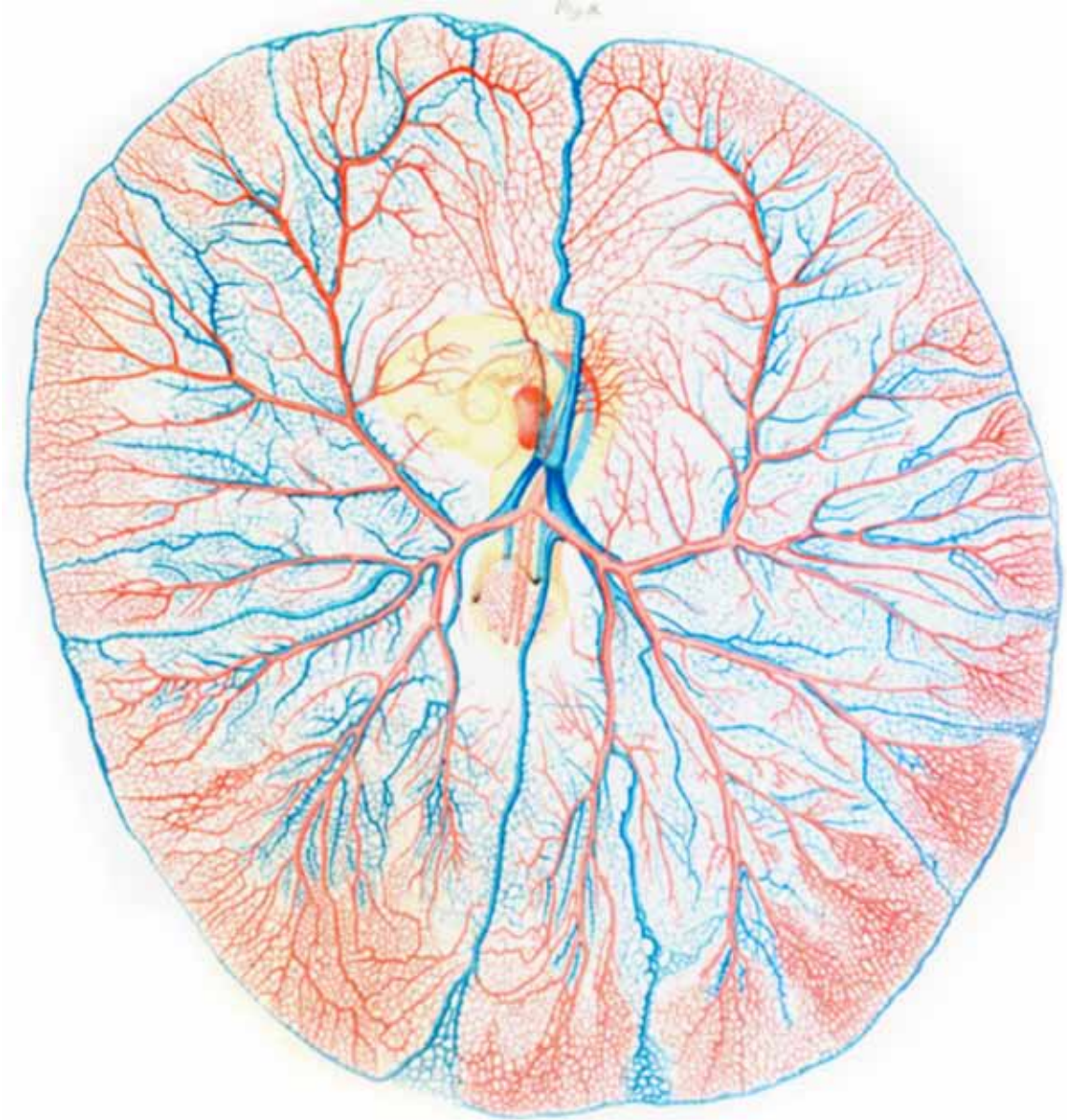
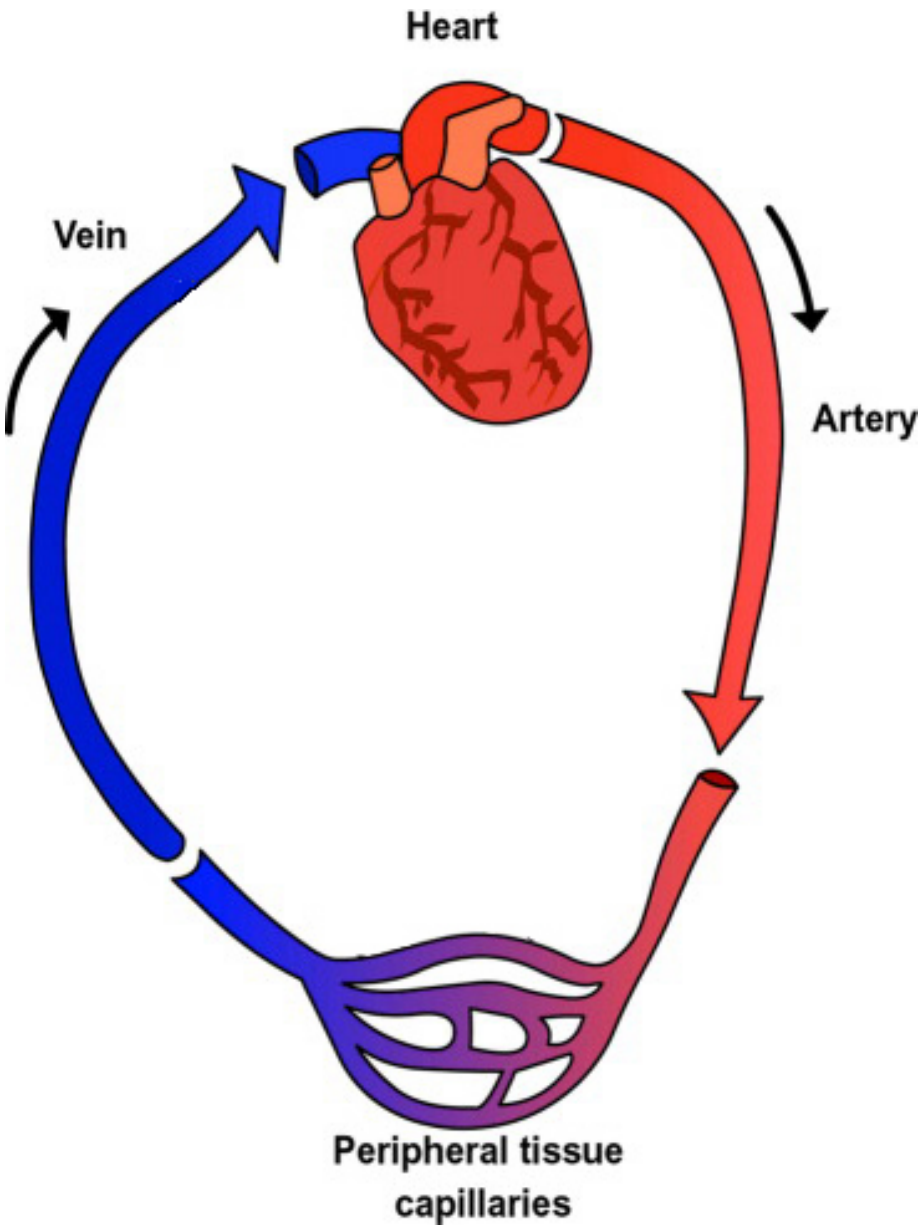


The Vasculature-
Some Basics

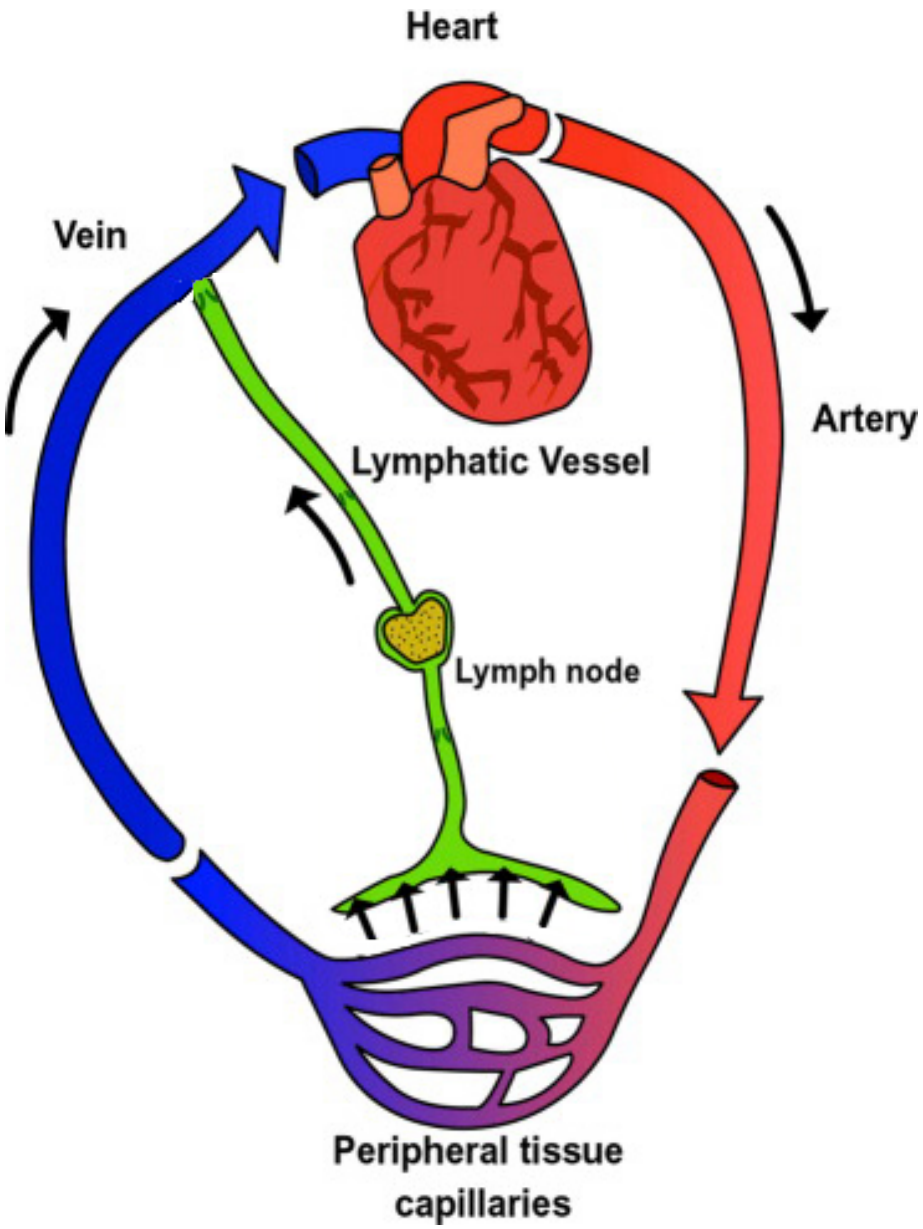
The Circulatory System



- Complex set of seamless interconnected tubes forming a continuously re-circulating loop
- Function: Transports oxygen, nutrients, hormonal signals, and immune system cells/factor, etc.
- Major vessels are reproducible and evolutionarily conserved
- Minor vessels are variable and plastic throughout life
- Associated pathologies include cardiovascular disease and cancer

Adapted from Hong YK. et.al., 2004

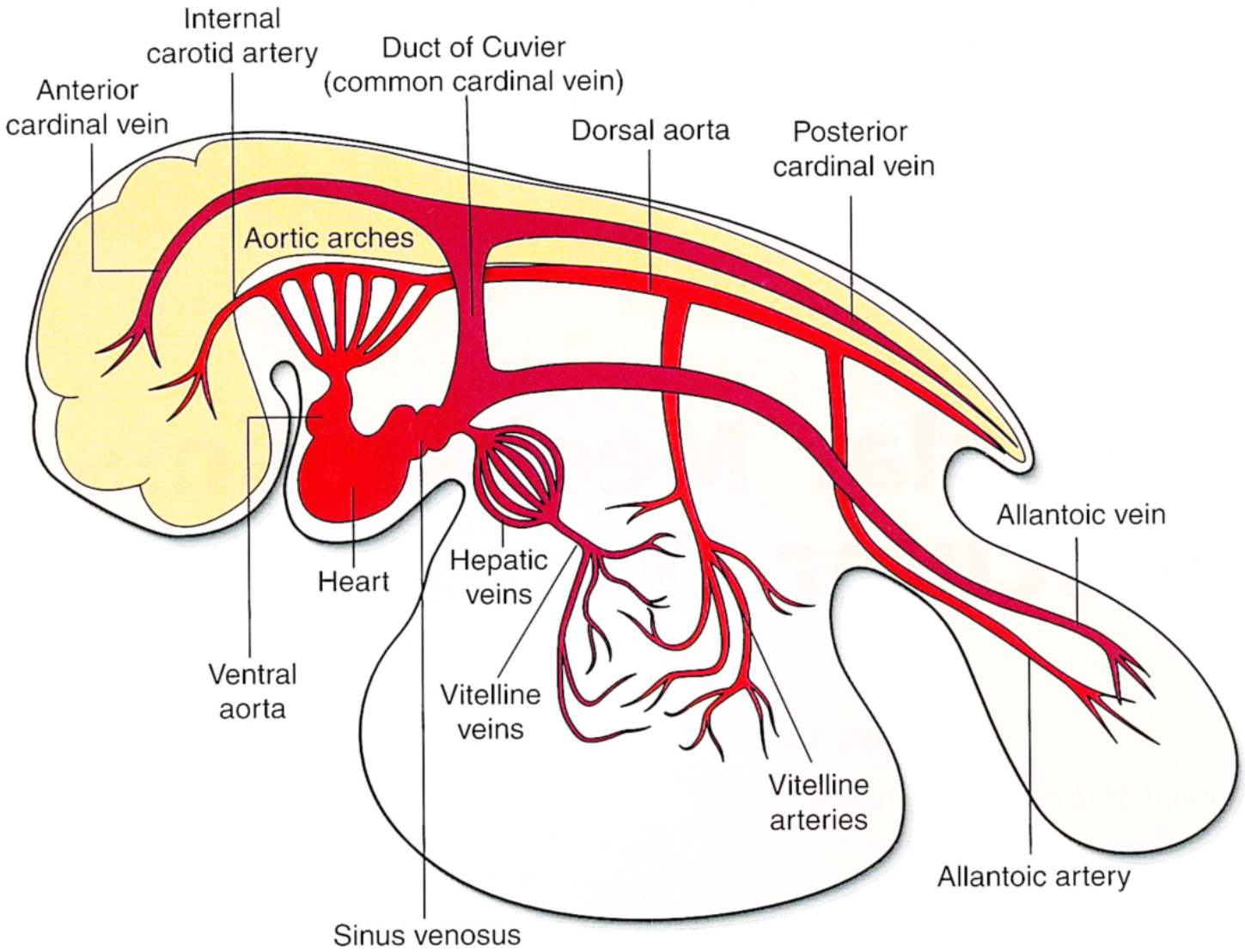
The Lymphatic System



- Complex set of interconnected tubes forming a blind-ended tree
- Function: fluid homeostasis, absorption of lipid from the intestinal tract, immune responses (transports WBC and antigens to lymphoid organs)
- Major vessels are reproducible and evolutionarily conserved
- Pattern of minor vessels is variable and plastic throughout the life on an animal
- Associated pathologies include Lymphedema and cancer metastasis

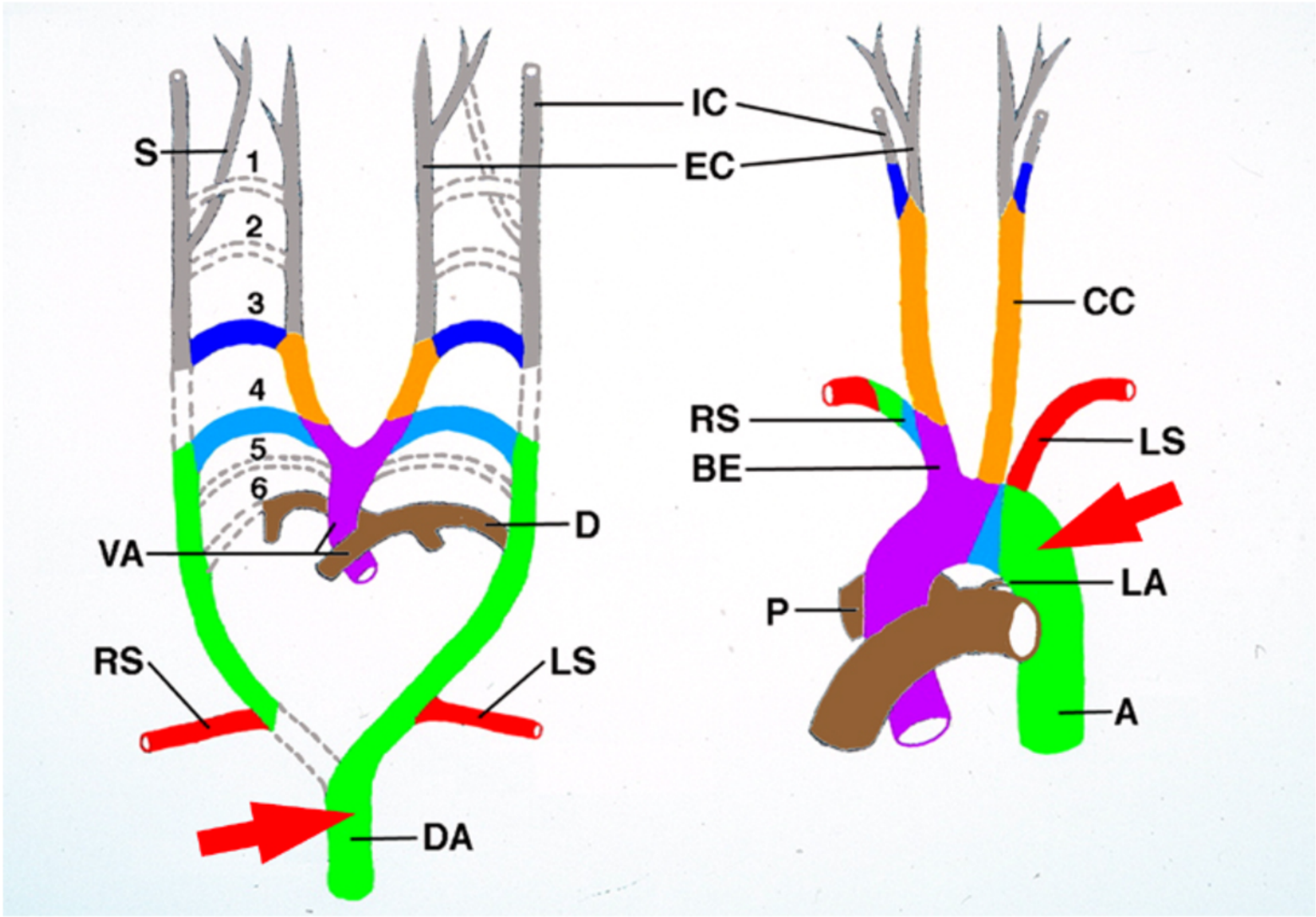
Adapted from Hong YK. et.al., 2004

The Developing Circulatory System



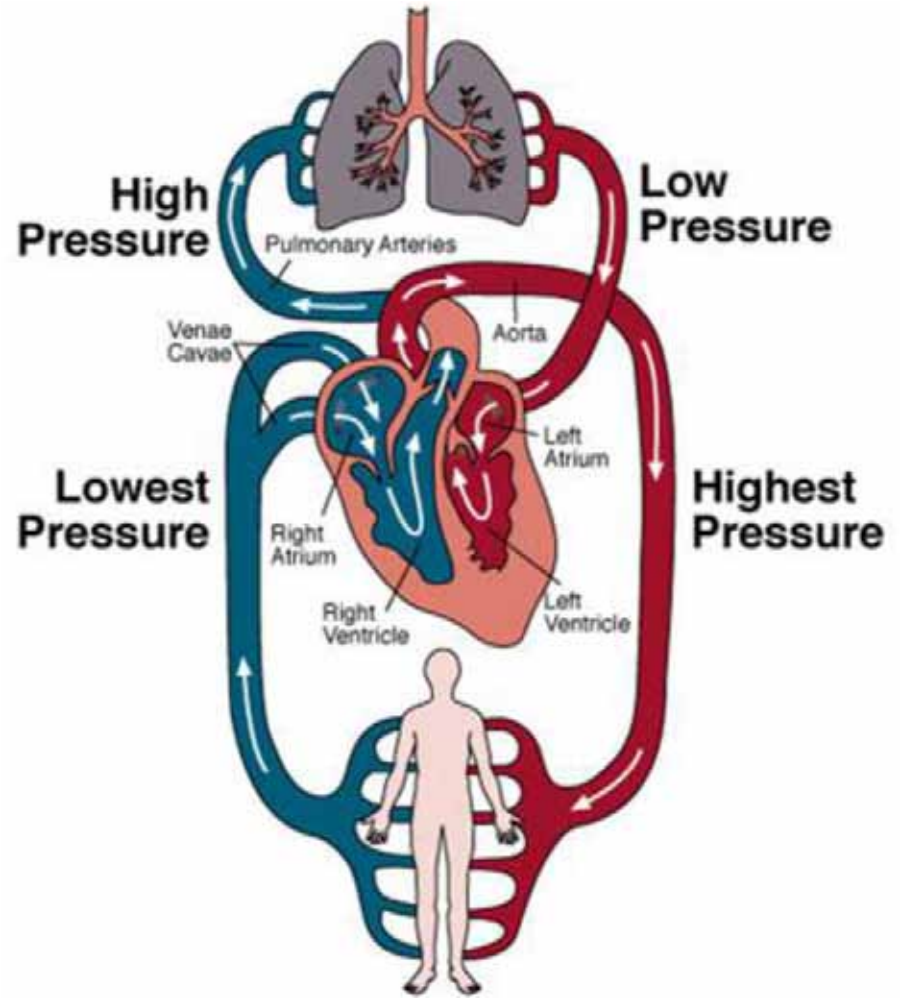
The Developing Circulatory System

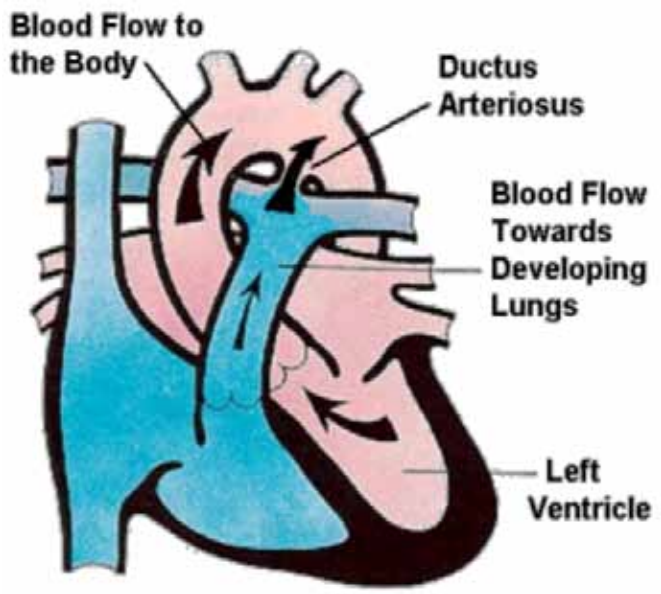
Aortic Arch Remodeling



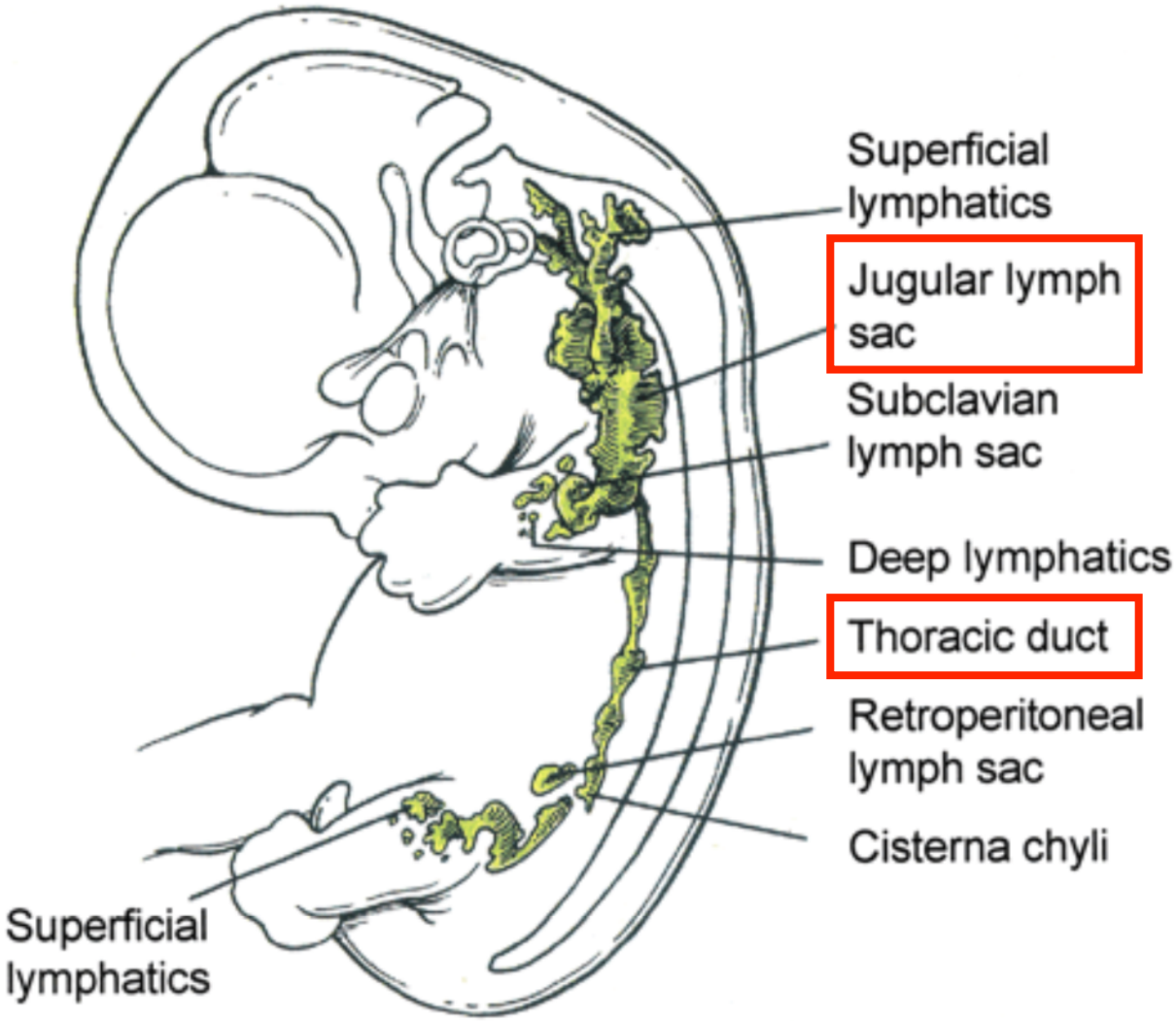
The Developing Circulatory System

Pulmonary Circulation

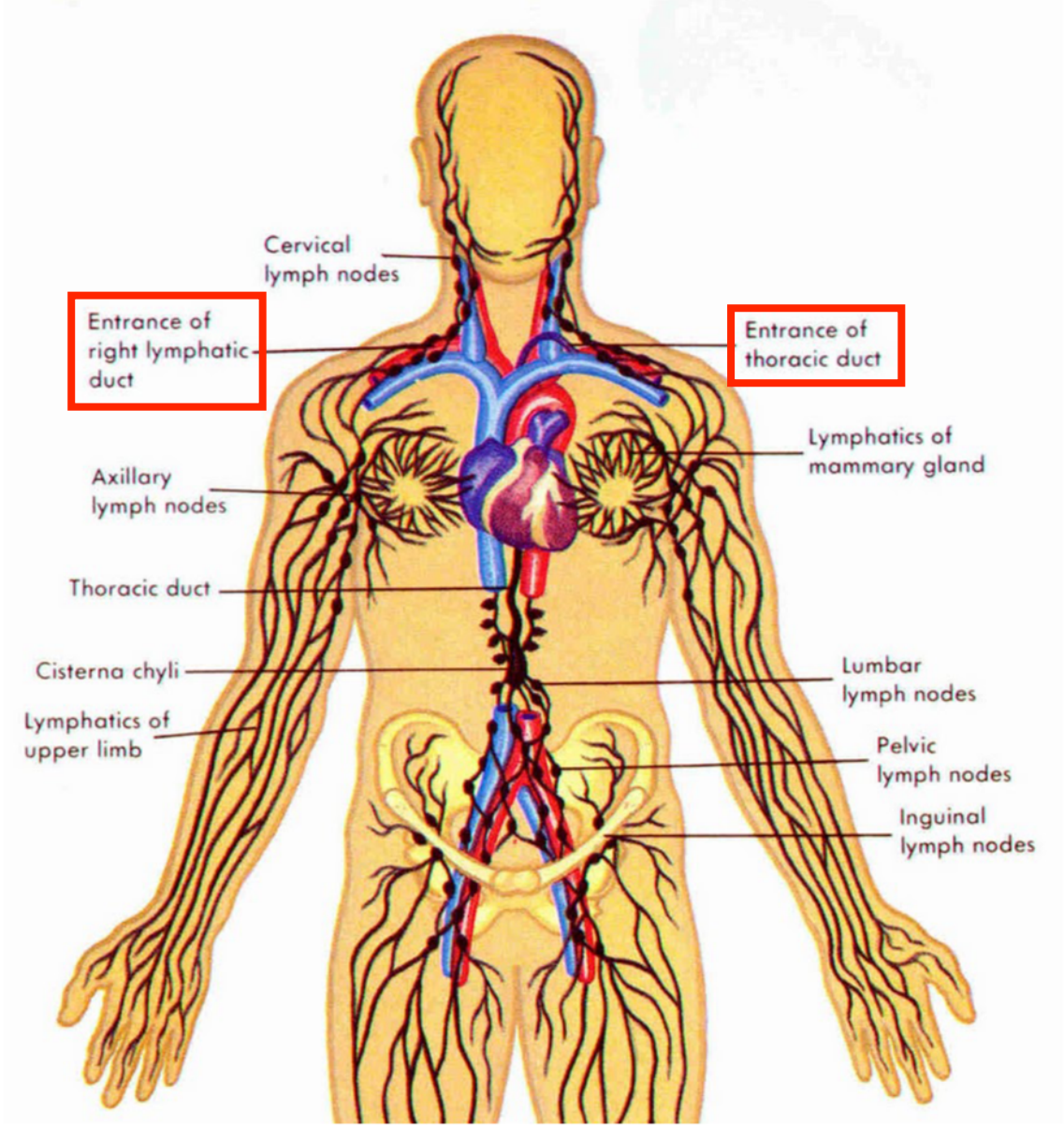




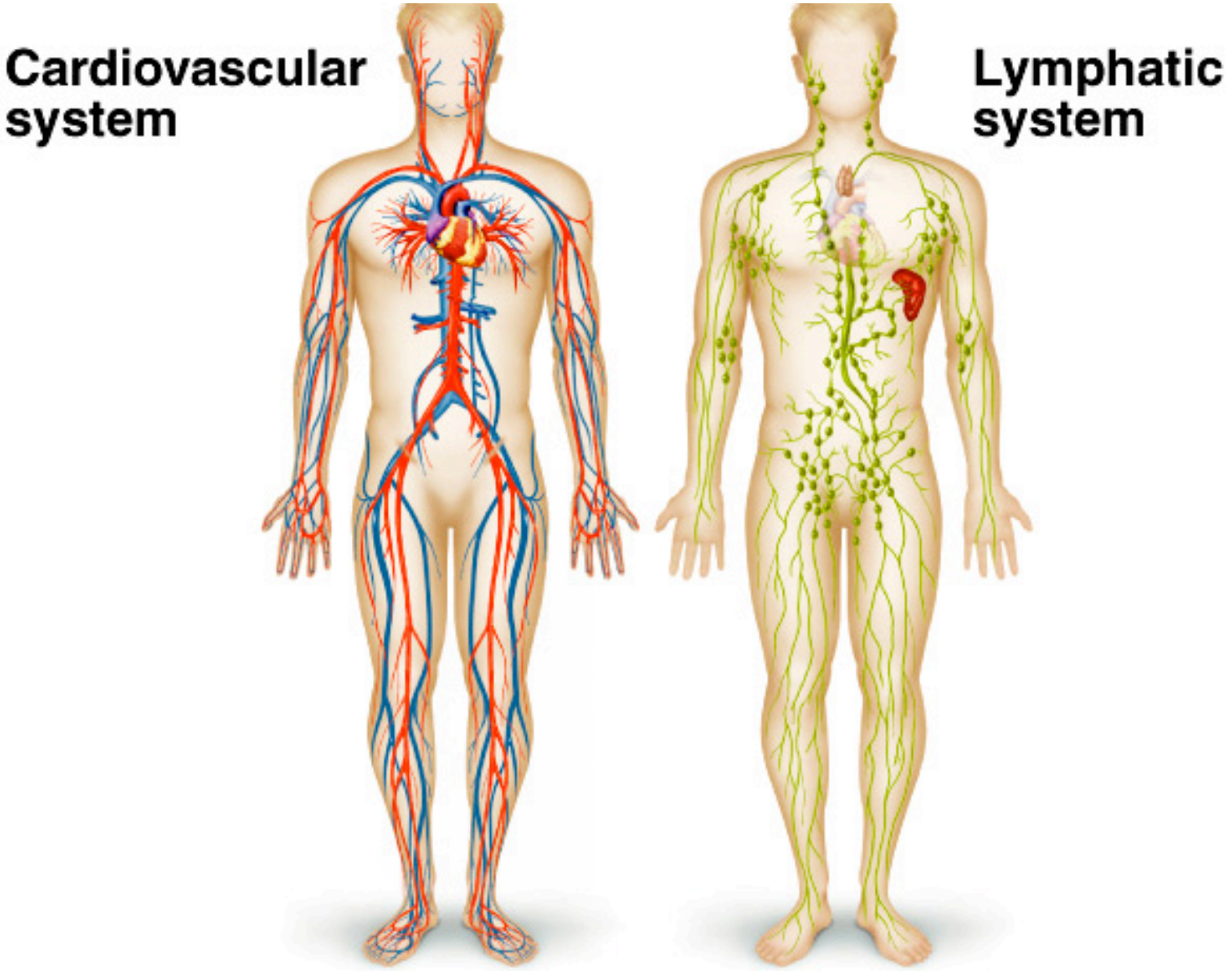
The Developing Lymphatic System



The Developing Lymphatic System



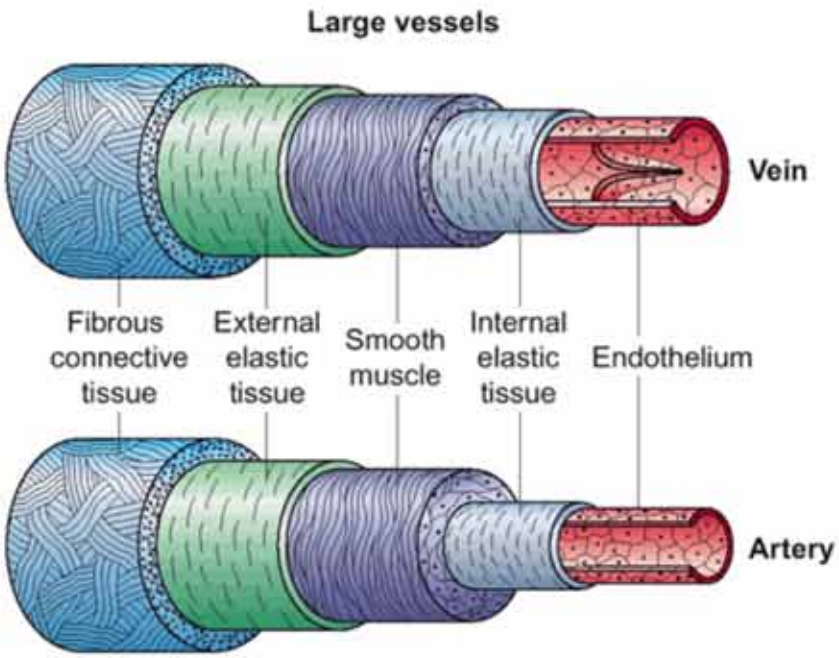
Anatomical correlation….

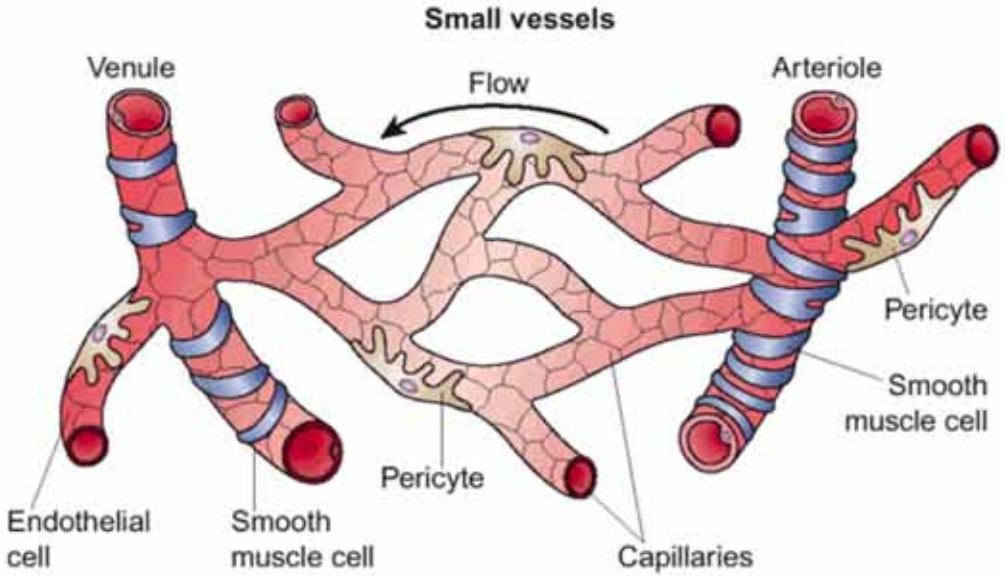


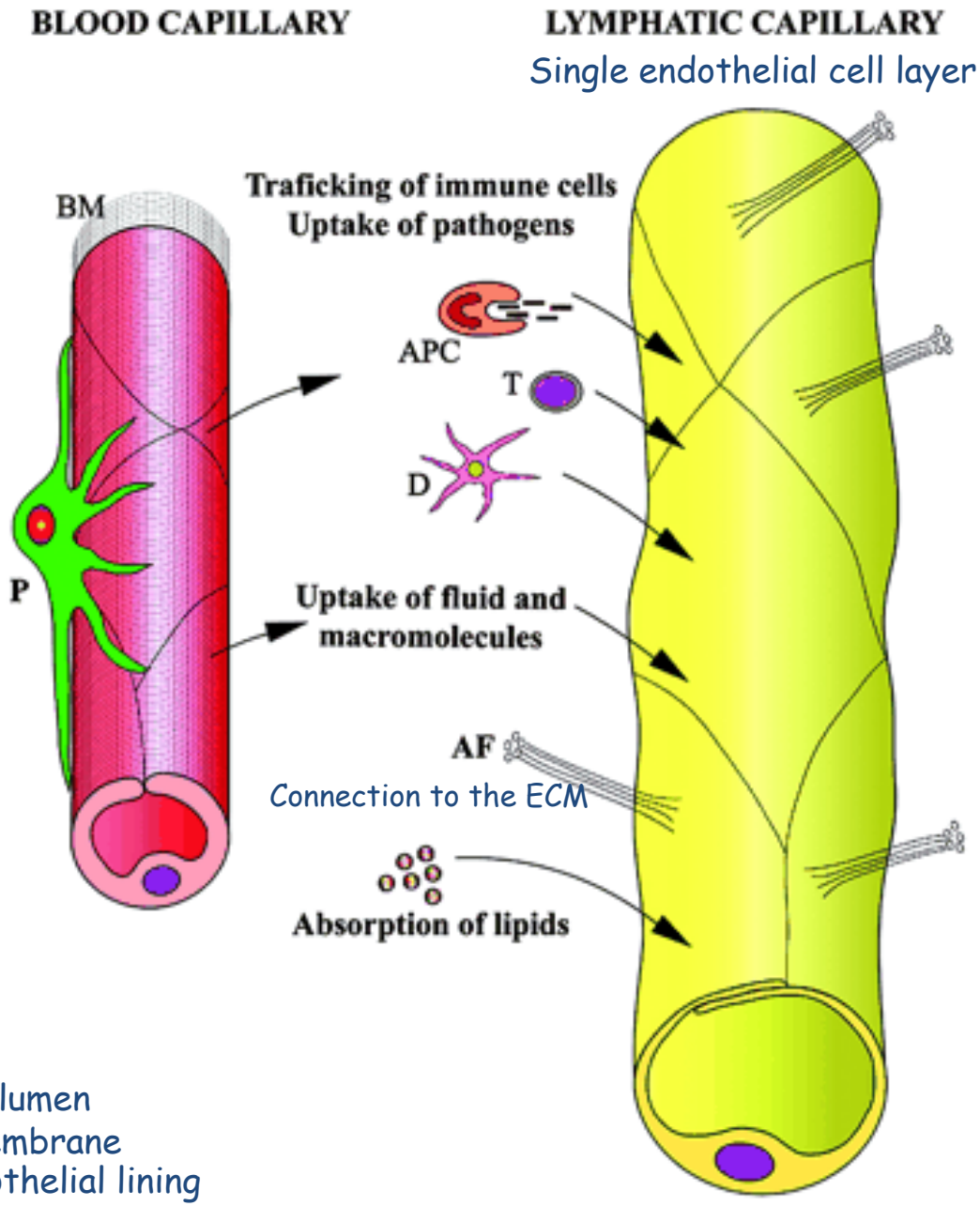
Vascular Cell Types

- Blood vessels are composed of **vascular endothelial cells (VEC)** and **vascular smooth muscle cells (VSMC)**
- **VEC:**
  - Mesodermal derivatives - earliest progenitors (“angioblasts”) arise in lateral mesoderm along with blood and pronephric progenitors
  - Very long lived
  - Can contribute to new blood vessels throughout life
  - Acquire distinct differentiated A-V & etc. identities and functions
- **VSMC:**
  - Origin of most VSMC is unclear - at least some cranial VSMC are neural crest derivatives
  - Undifferentiated VSMC are secretory cells, differentiated VSMC are non-secretory contractile cells
  - Differentiation of VSMC is readily reversible

Veins and Arteries







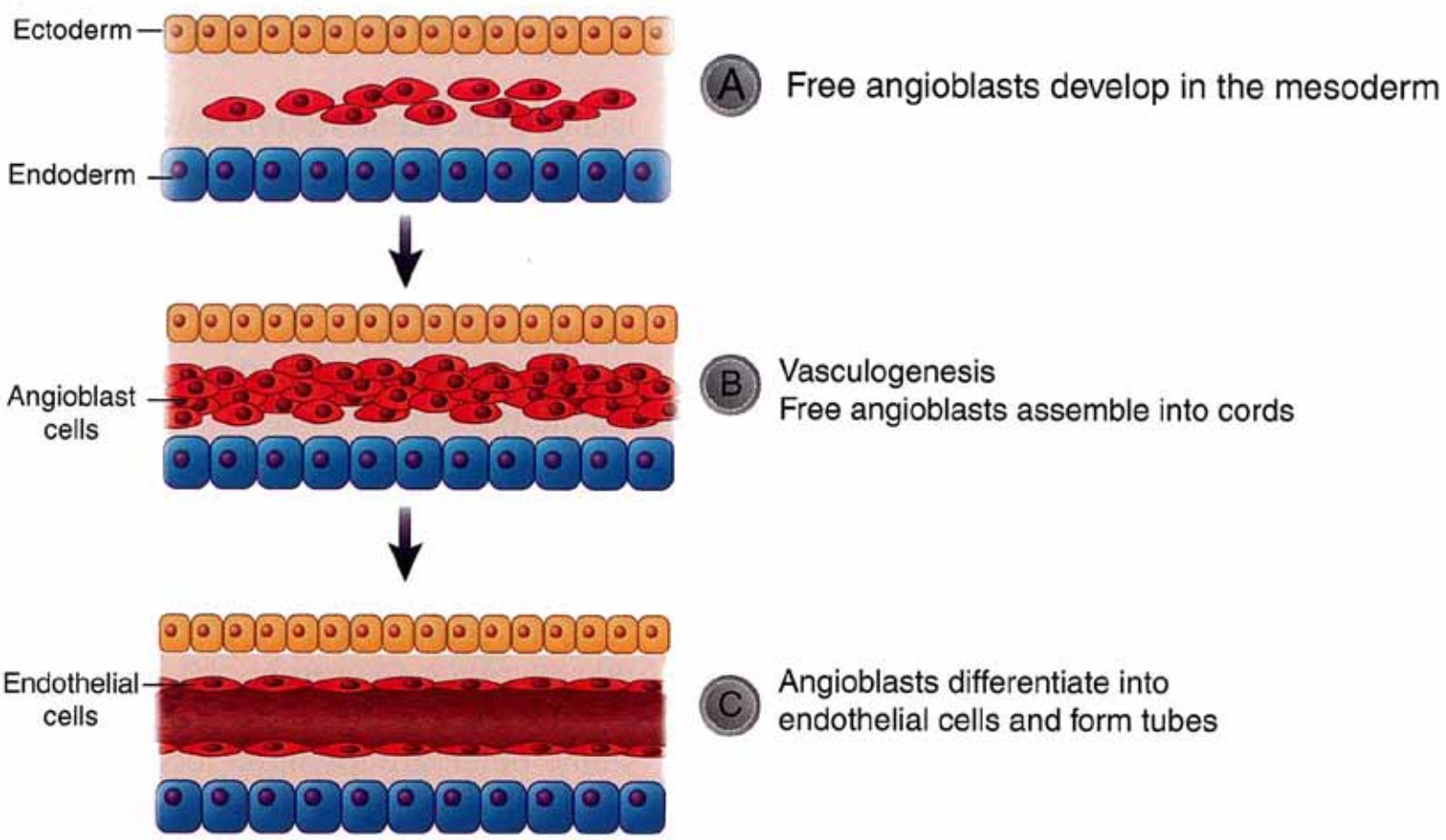
Lymphatics:

1. Irregular and wider lumen
2. Absence of basal membrane
3. Porous and thin endothelial lining
4. Anchoring filaments, prevent vessel collapse when interstitial pressure rises
5. Usually observed in a fully or partially collapsed state

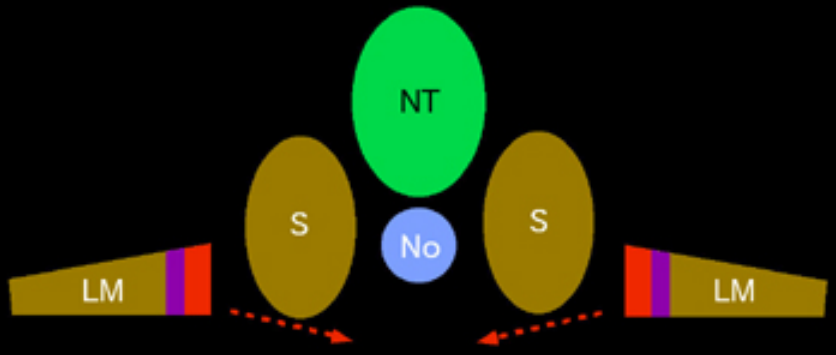
Pepper et al., 2003

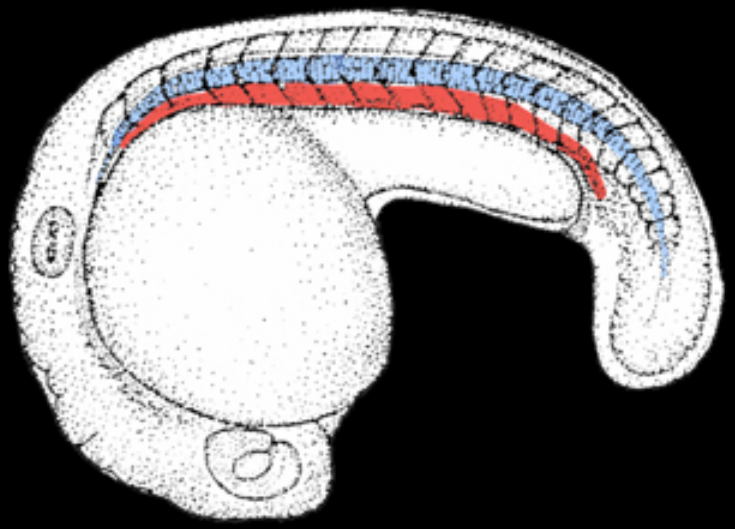
Origins of the Vasculature

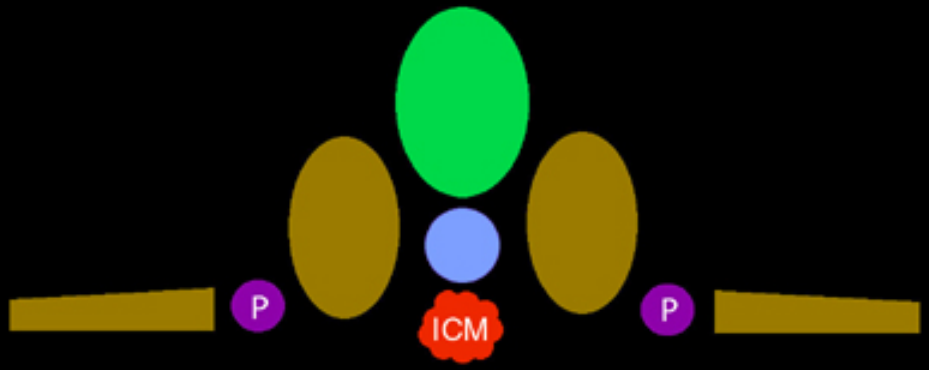
Endothelial Specification and Vasculogenesis

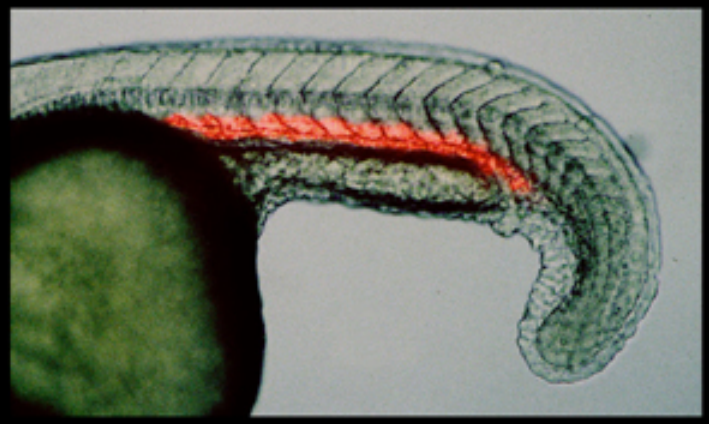


Early vascular and hematopoietic progenitors arise in the lateral mesoderm





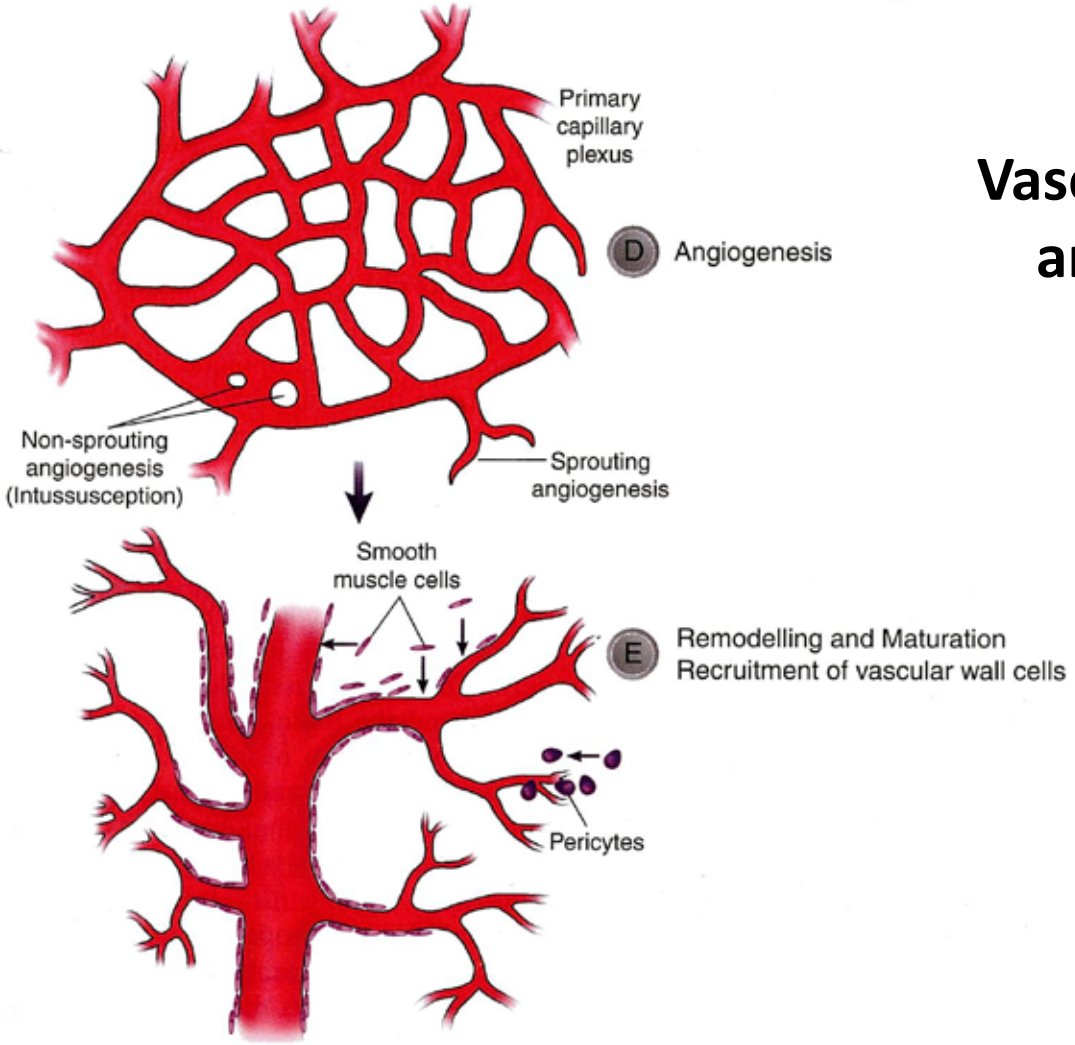




Formation of Intermediate Cell Mass (ICM), which gives rise to both blood and vascular endothelial tissues

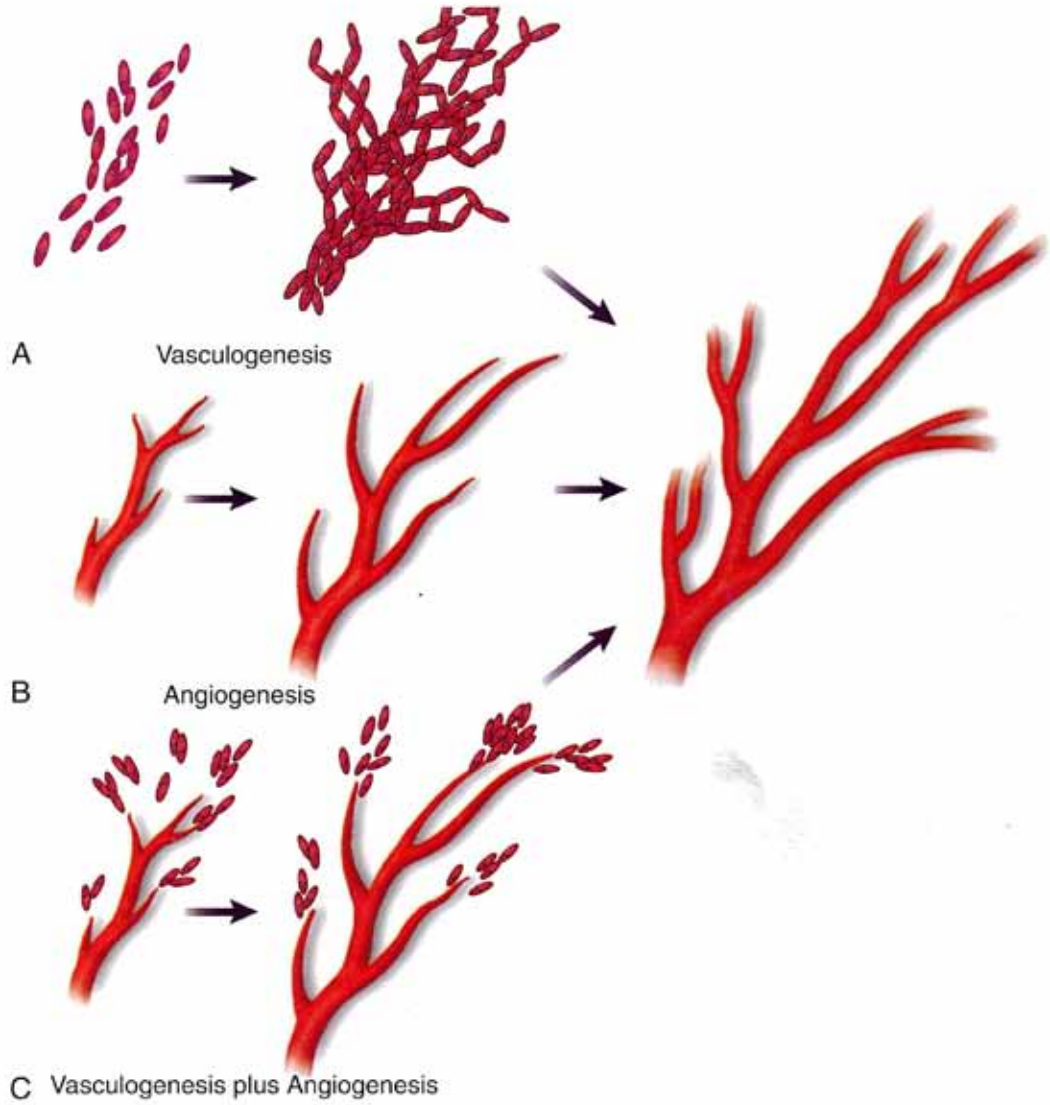
ICM in zebrafish; diagram (TOP) and autofluorescent blood cells in ICM of a *dracula* mutant embryo

Origins of the Vasculature



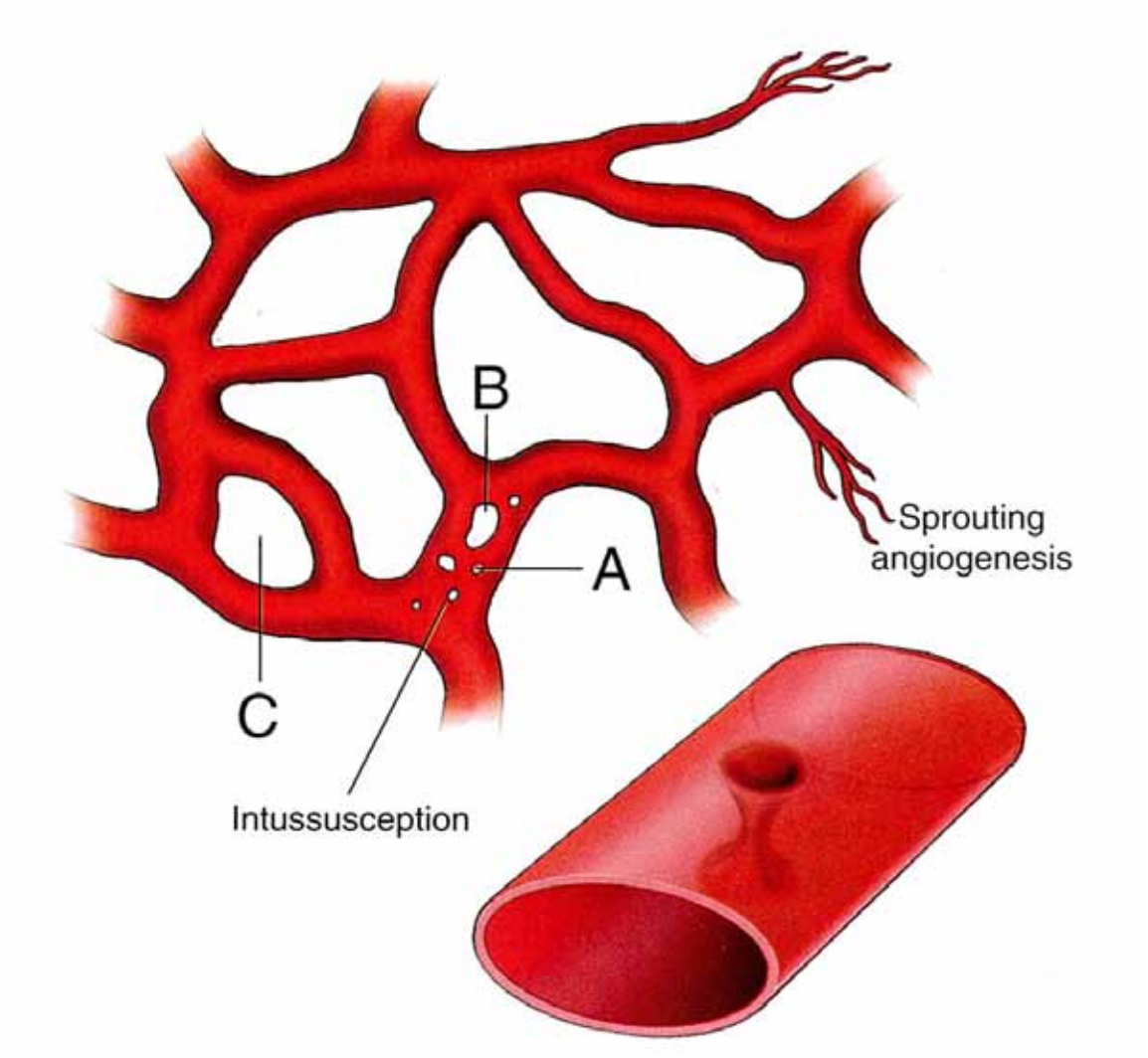
Vascular Remodeling and Maturation; Angiogenesis

Origins of the Vasculature



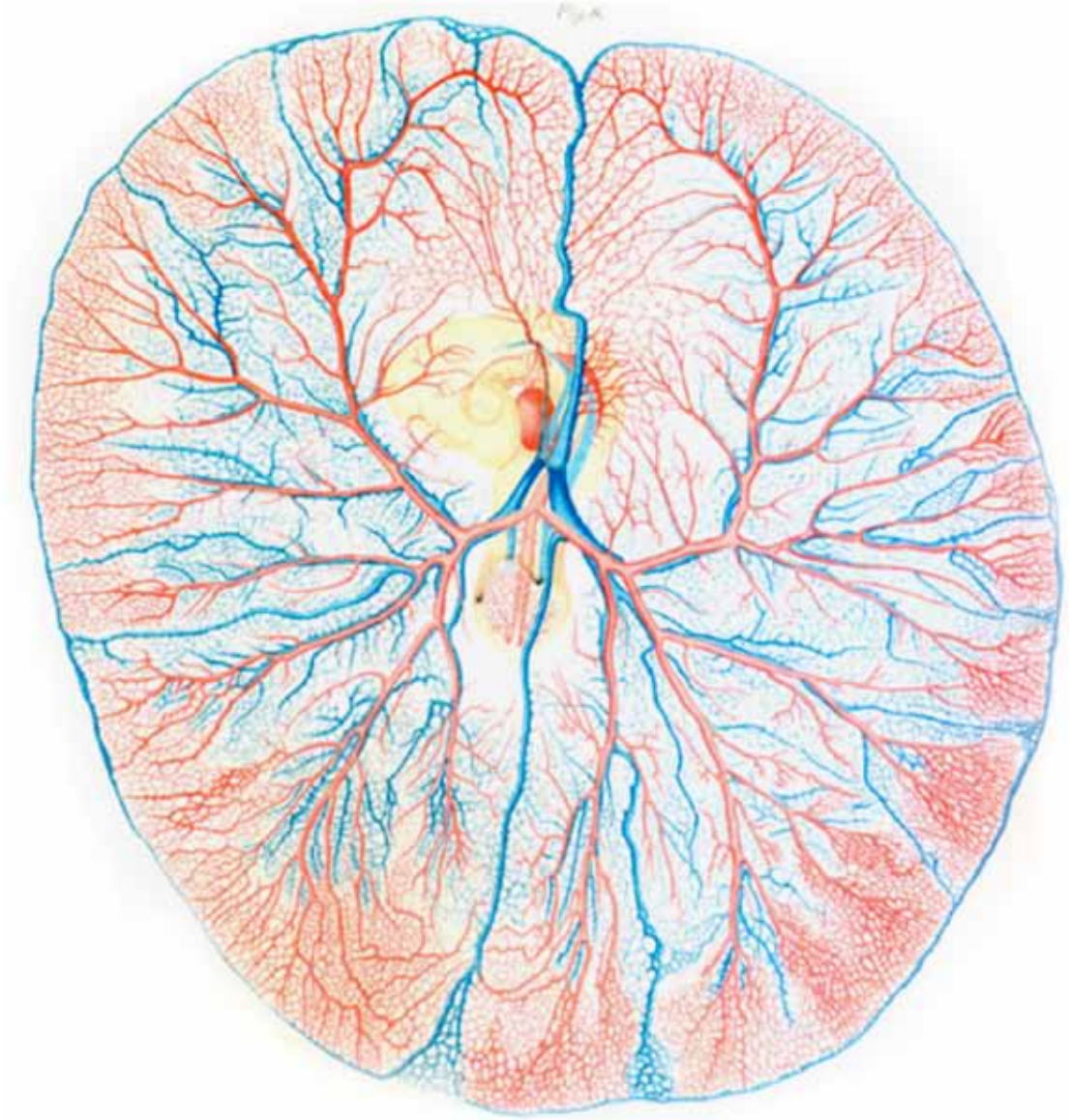
Vasculogenesis
vs.
Angiogenesis

Origins of the Vasculature



Intussusceptive
vs.
Sprouting
Angiogenesis

Origins of the Vasculature



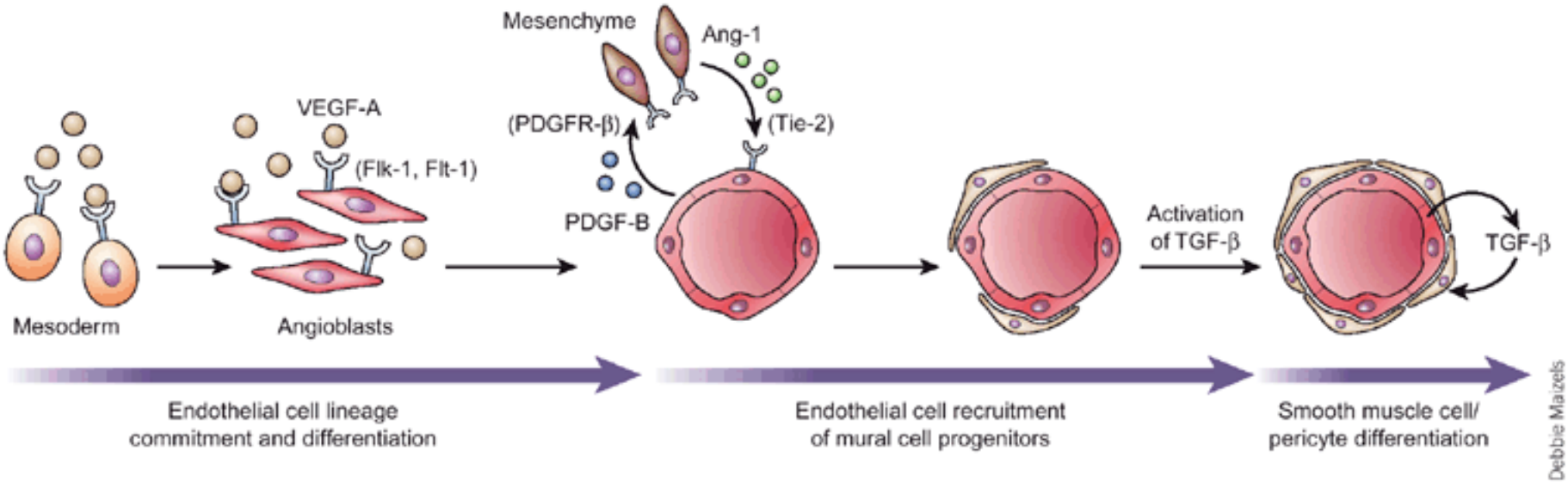
Avian yolk sac primitive vascular plexus

Popoff, 1895

Molecular Regulation of Vessel Formation- Key Players

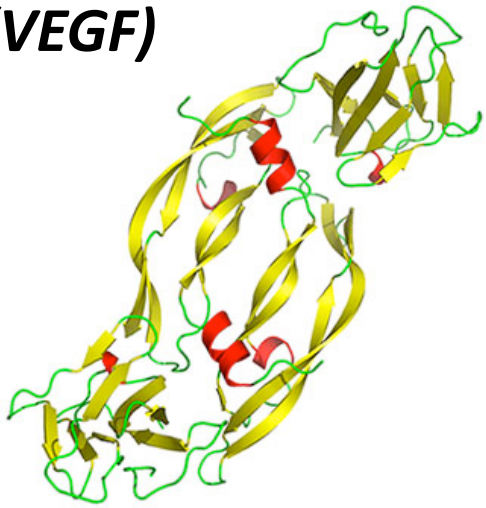
Molecular Regulation of Vessel Formation

Endothelial signaling during development



Molecular Regulation of Vessel Formation

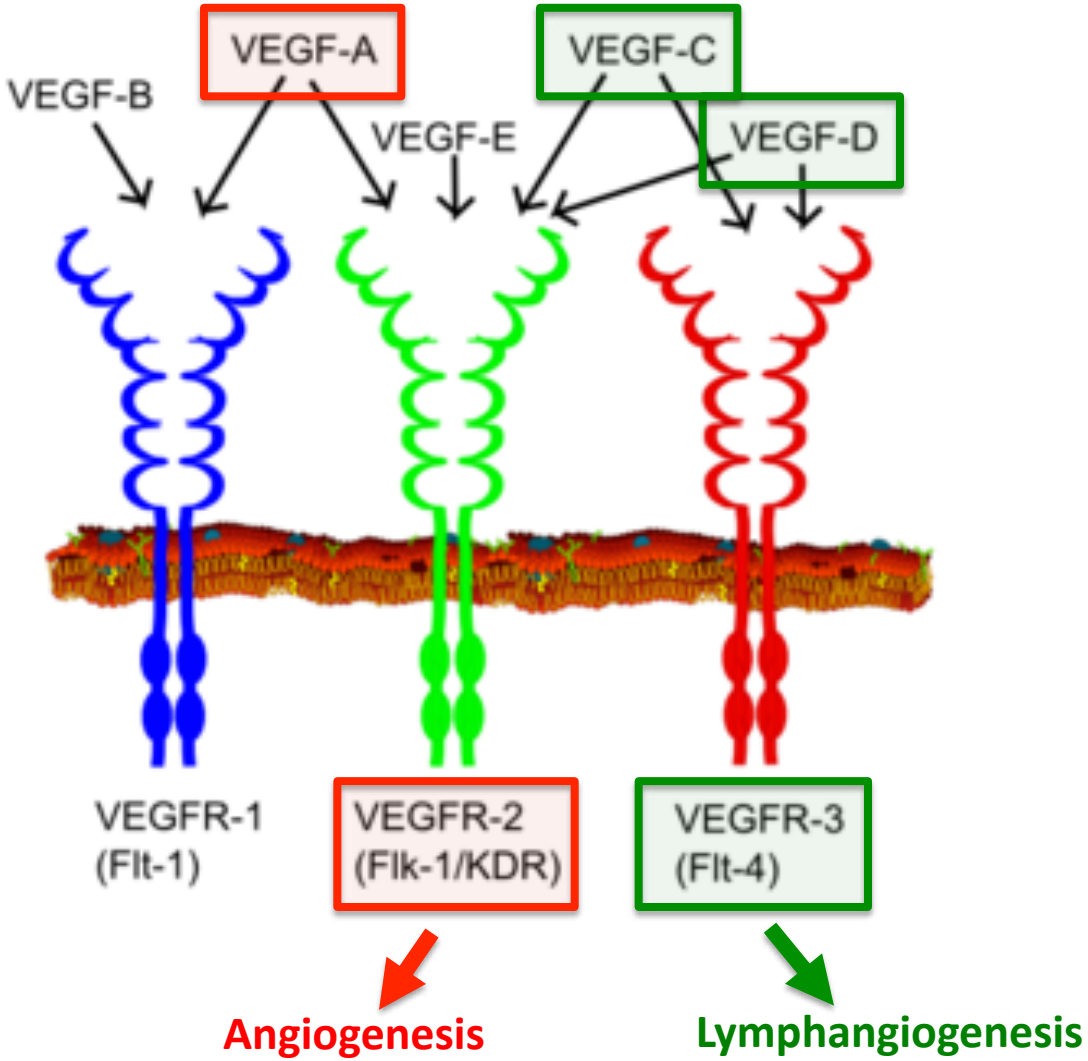
Vascular Endothelial Growth Factor (VEGF)



- **Signaling protein produced by various cells, that stimulates vasculogenesis and angiogenesis**
- **VEGF is absolutely required for endothelial specification, differentiation (arterial), migration, and survival.**
- **Genetically programmed VEGF production drives vessel formation during development**
- **Hypoxia and nutritional stress induce VEGF production to promote vessel growth during later development and postnatal life**
- **Anti-VEGF therapies are being used to inhibit pathological vessel growth in age-related macular degeneration and cancer. These can involve monoclonal antibodies such as bevacizumab (Avastin) or orally-available small molecules that inhibit the tyrosine kinases stimulated by VEGF such as sunitinib (Sutent).**

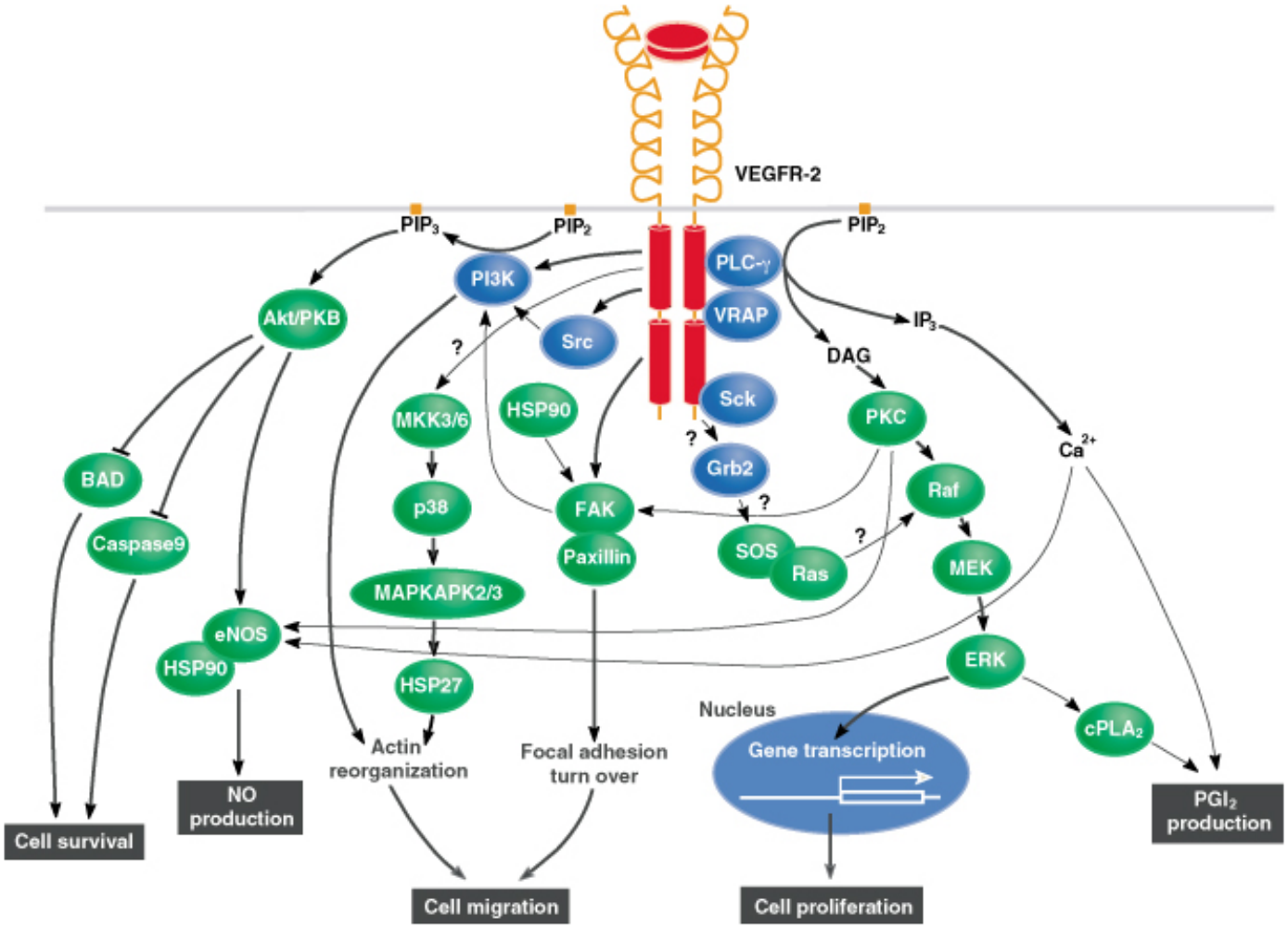
Molecular Regulation of Vessel Formation

Vascular Endothelial Growth Factor (VEGF) – Ligands & Receptors



Molecular Regulation of Vessel Formation

Vascular Endothelial Growth Factor (VEGF) – Intracellular SIgnaling



Molecular Regulation of Vessel Formation

Angiopoietins and Their Receptors

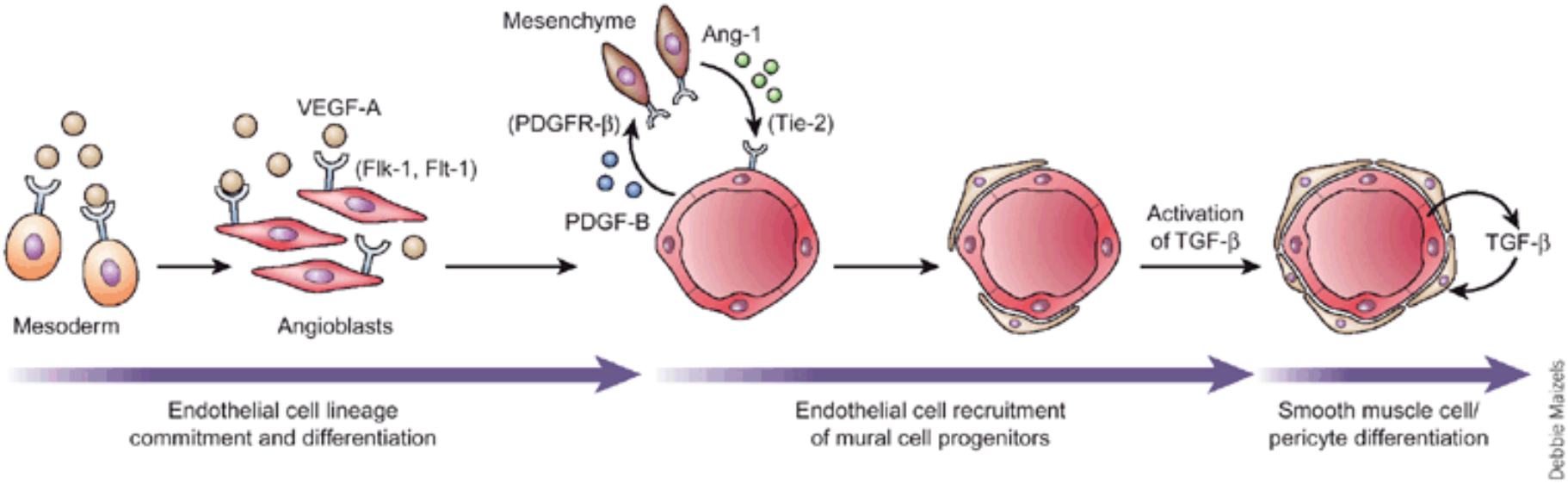
- **Signaling proteins produced by various cells, especially pericytes & vascular smooth muscle cells**
- **Act through "Tie" tyrosine kinase receptors, esp. Tie-2**
- **Promote vascular maturation, provide trophic support for the mature endothelium (major smooth muscle-derived factor playing this role?)**
- **Hypothesis: low ANG + high VEGF→ vascular growth, low ANG + low VEGF → vascular regression**
- **Also considered as a possible anti-angiogenic therapeutic target**

Molecular Regulation of Vessel Formation

Platelet-Derived Growth Factor (PDGF)

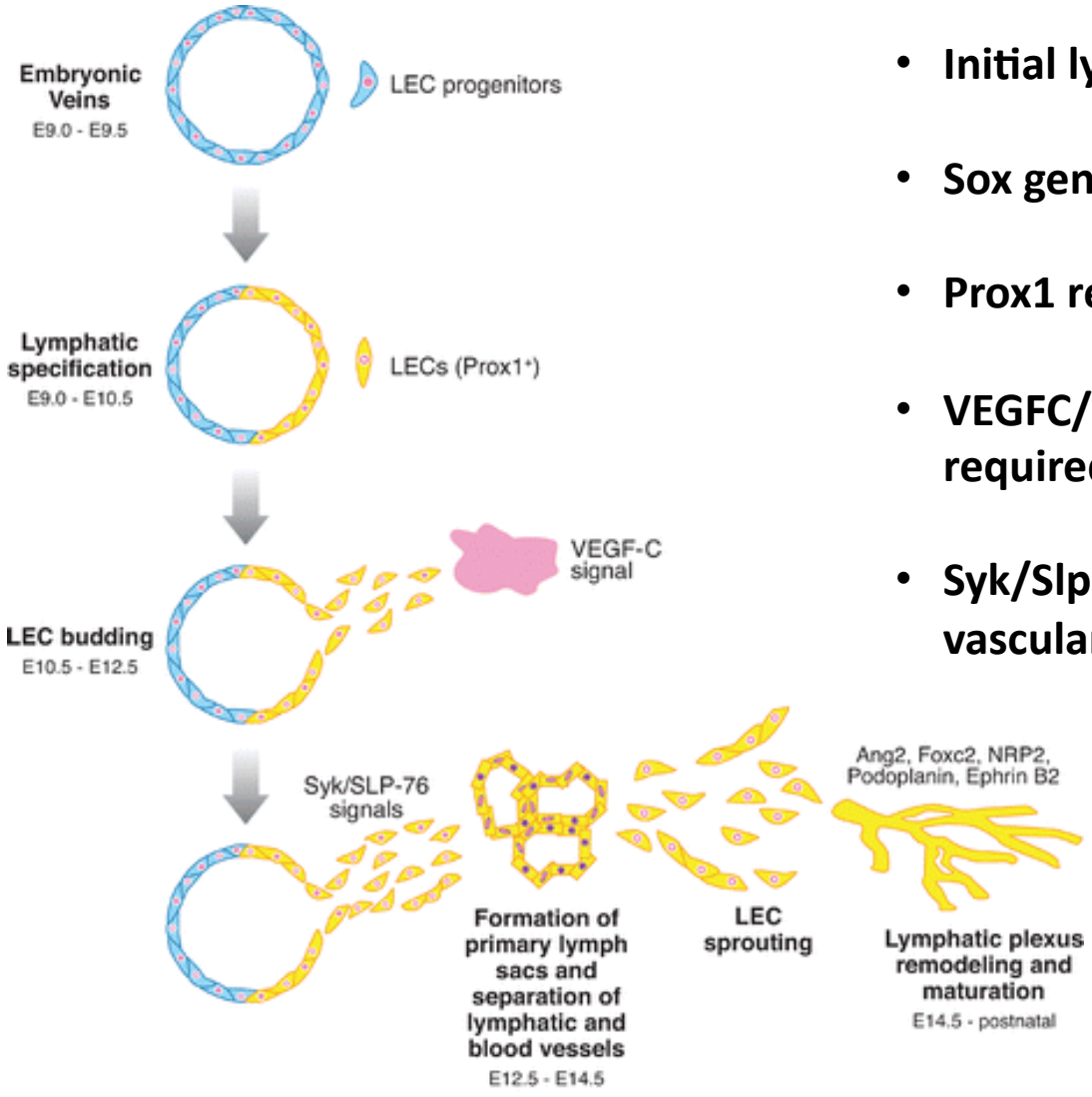
- **Potent mitogen for smooth muscle cells and glial cells via tyrosine kinase PDGF receptors (PDGFRs)**

- **Variety of isoforms, some produced by endothelium to promote pericyte and smooth muscle investment of the vessels, promoting vessel maturation.**



Molecular Regulation of Vessel Formation

Specification of Lymphatic Vessels

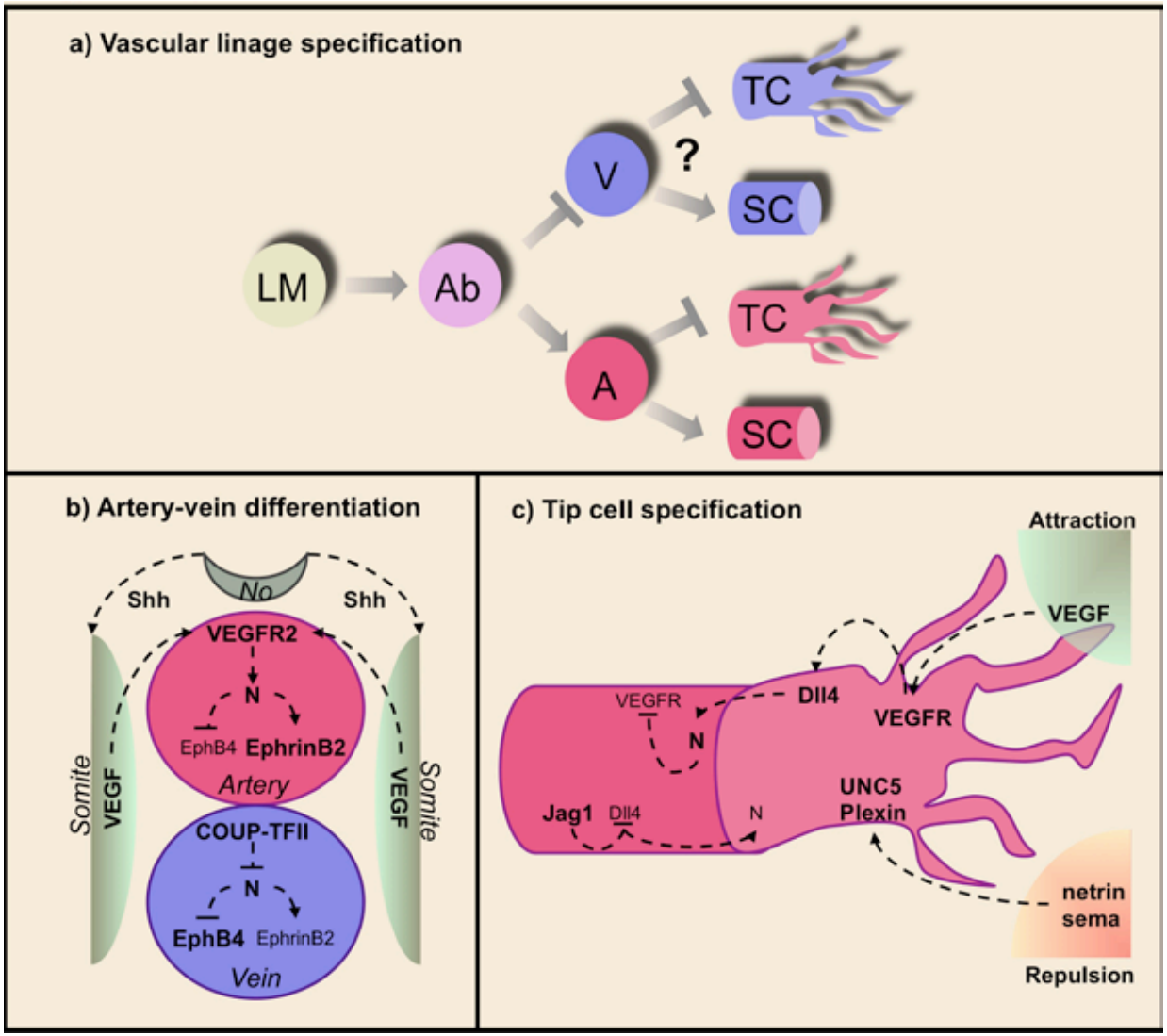


Oliver G, Alitalo K. 2005.
Annu. Rev. Cell Dev. Biol. 21:457–83

- **Initial lymphatic EC come from venous EC**
- **Sox genes "prespecify" venous EC to LEC**
- **Prox1 required to initiate and maintain LEC**
- **VEGFC/D drives LEC migration and growth, required for lymphangiogenesis**
- **Syk/Slp-76 required for blood/lymphatic vascular separation**

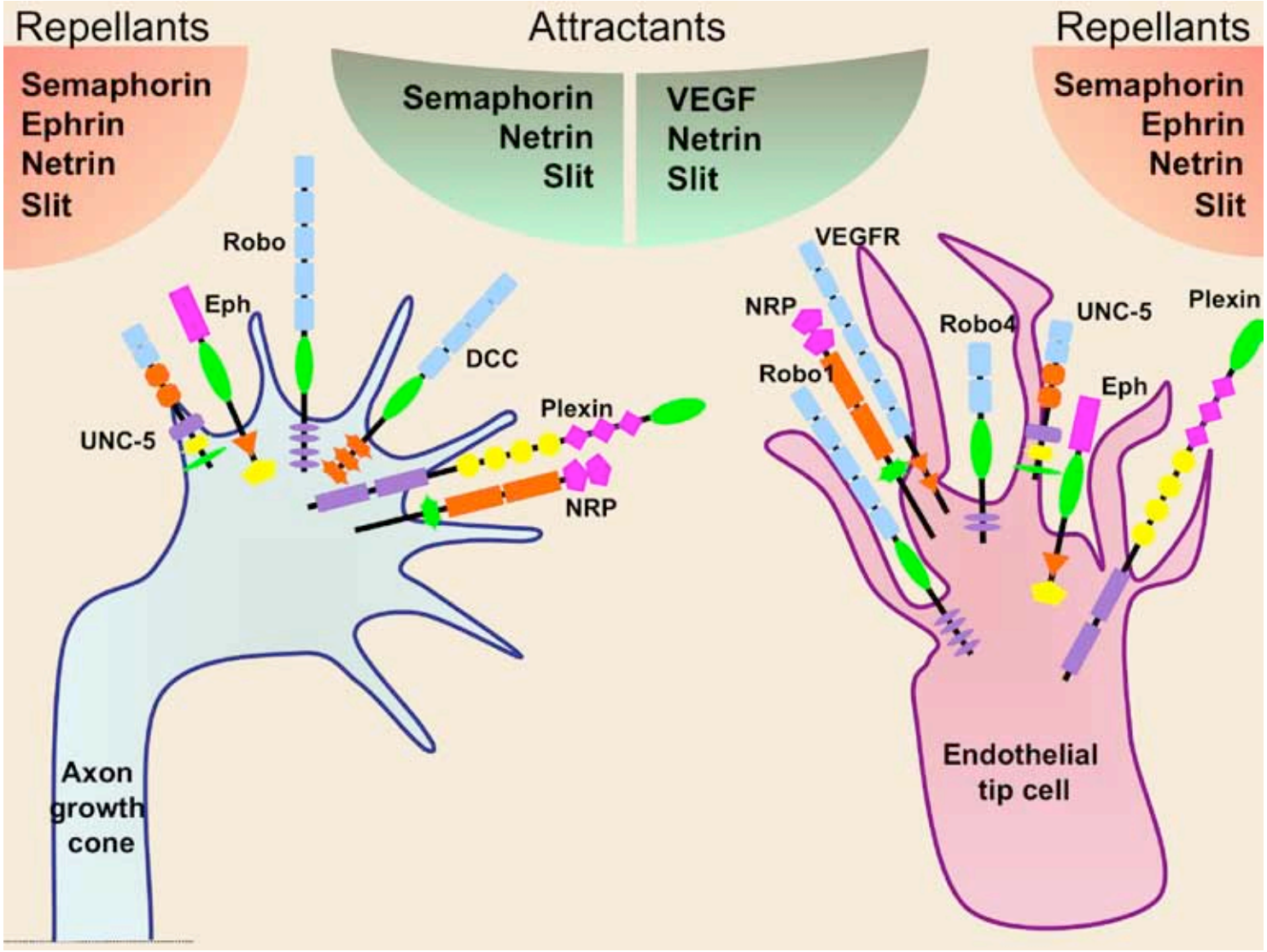
Molecular Regulation of Vessel Formation

Roles for Notch Signaling during EC Specification and Differentiation



Molecular Regulation of Vessel Formation

Neuronal Guidance Factors and Vascular Patterning



The Vasculature and Human Health

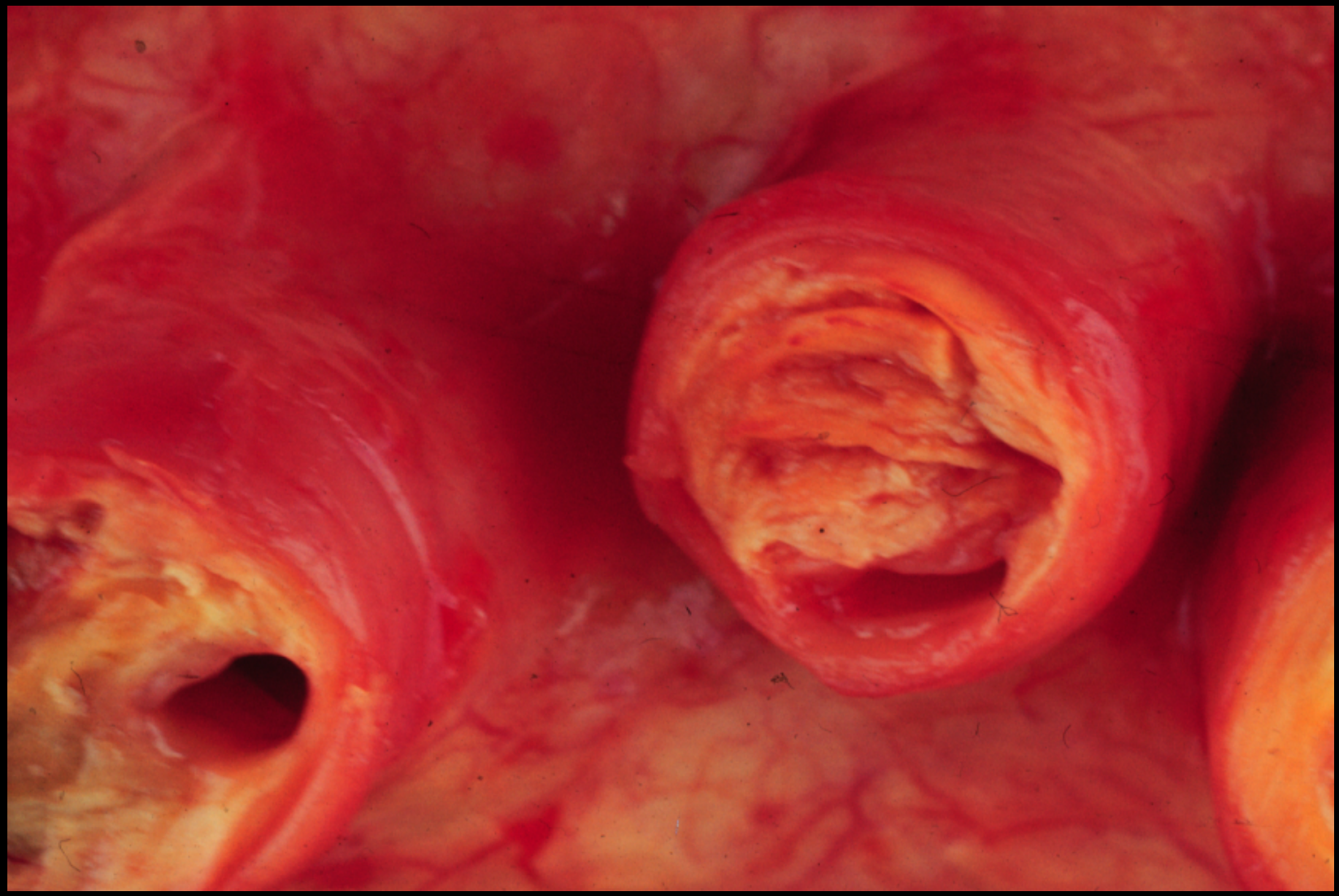
The Vasculature and Human Health

- Congenital or acquired vascular defects are responsible for the vast majority of mortality and morbidity in the Western world.
- These defects include atherosclerotic heart disease, vascular ischemia and stroke, and congenital heart and vascular defects.
- Blood vessels are also critical for tumor growth and progression, making them important therapeutic targets for cancer.

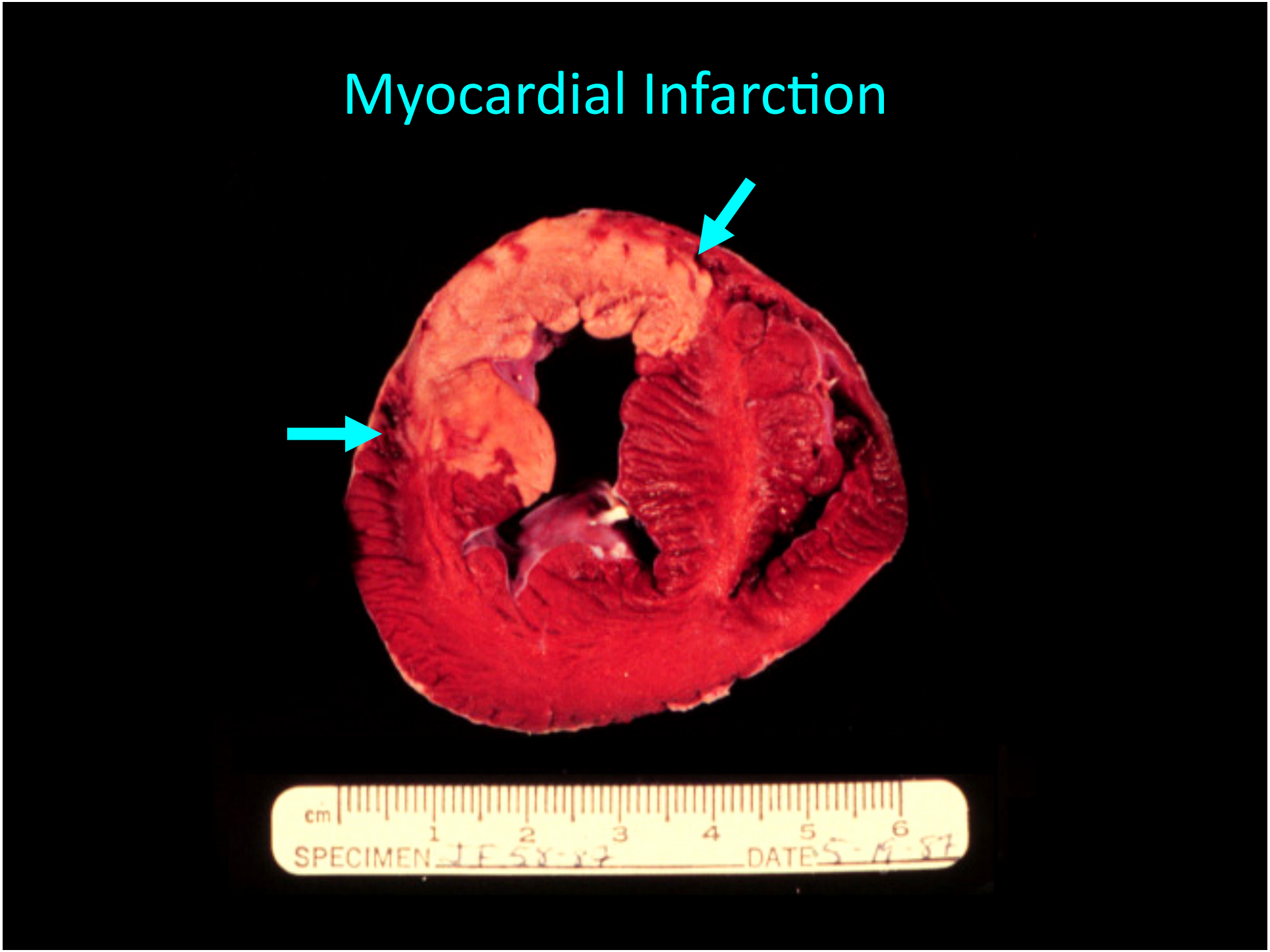
Blood Vessels and Heart Disease

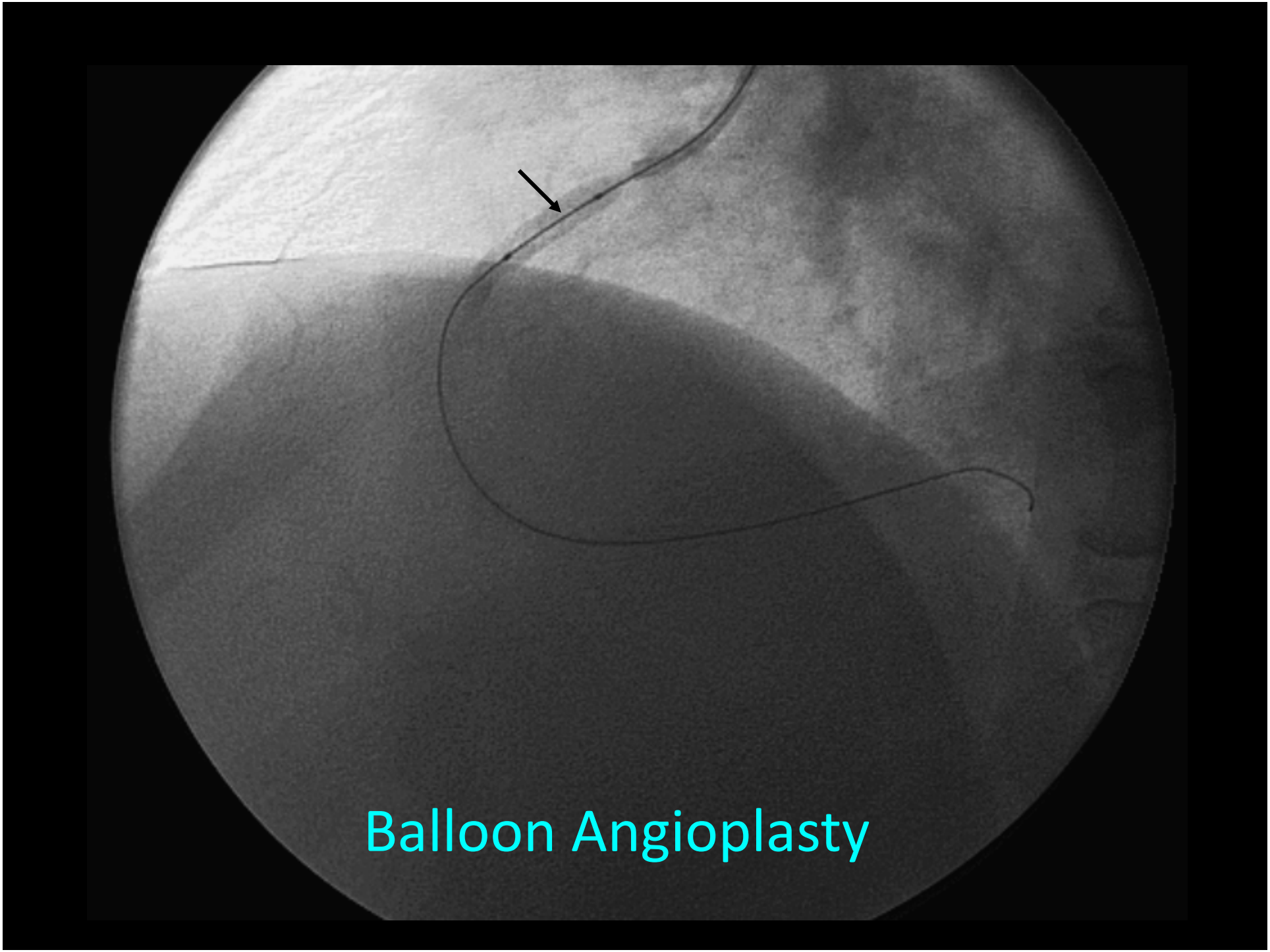
- Atherosclerotic heart disease is the major cause of death in the United States.
- Vessels blocked by atherosclerotic plaques can be opened by angioplasty, but frequently re-blockage ("restenosis") occurs due to overproliferation of vascular wall smooth muscle cells.
- The biology of atherosclerotic plaque formation and of vascular restenosis is still not well understood.

Atherosclerotic Coronary Arteries

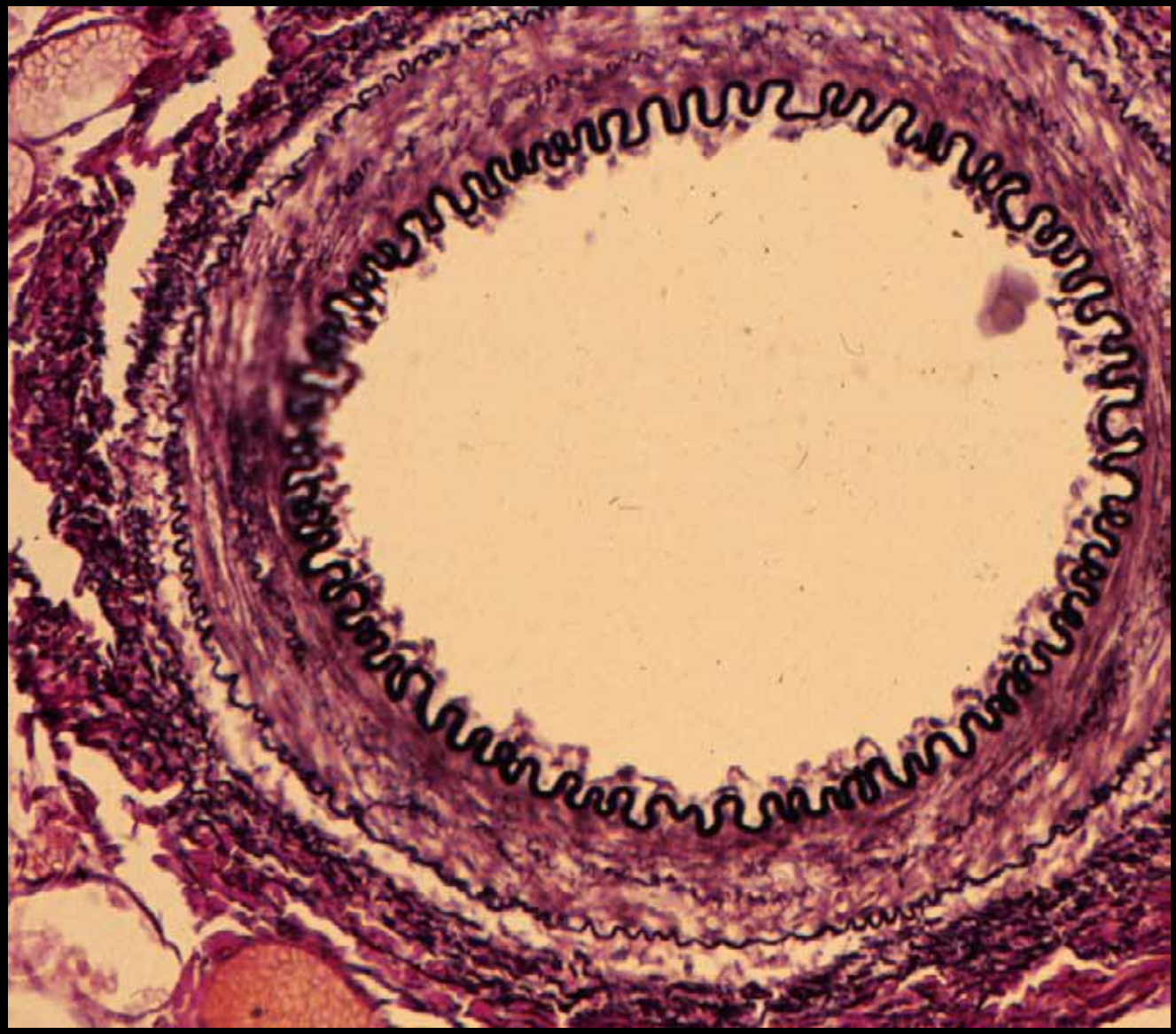


Myocardial Infarction

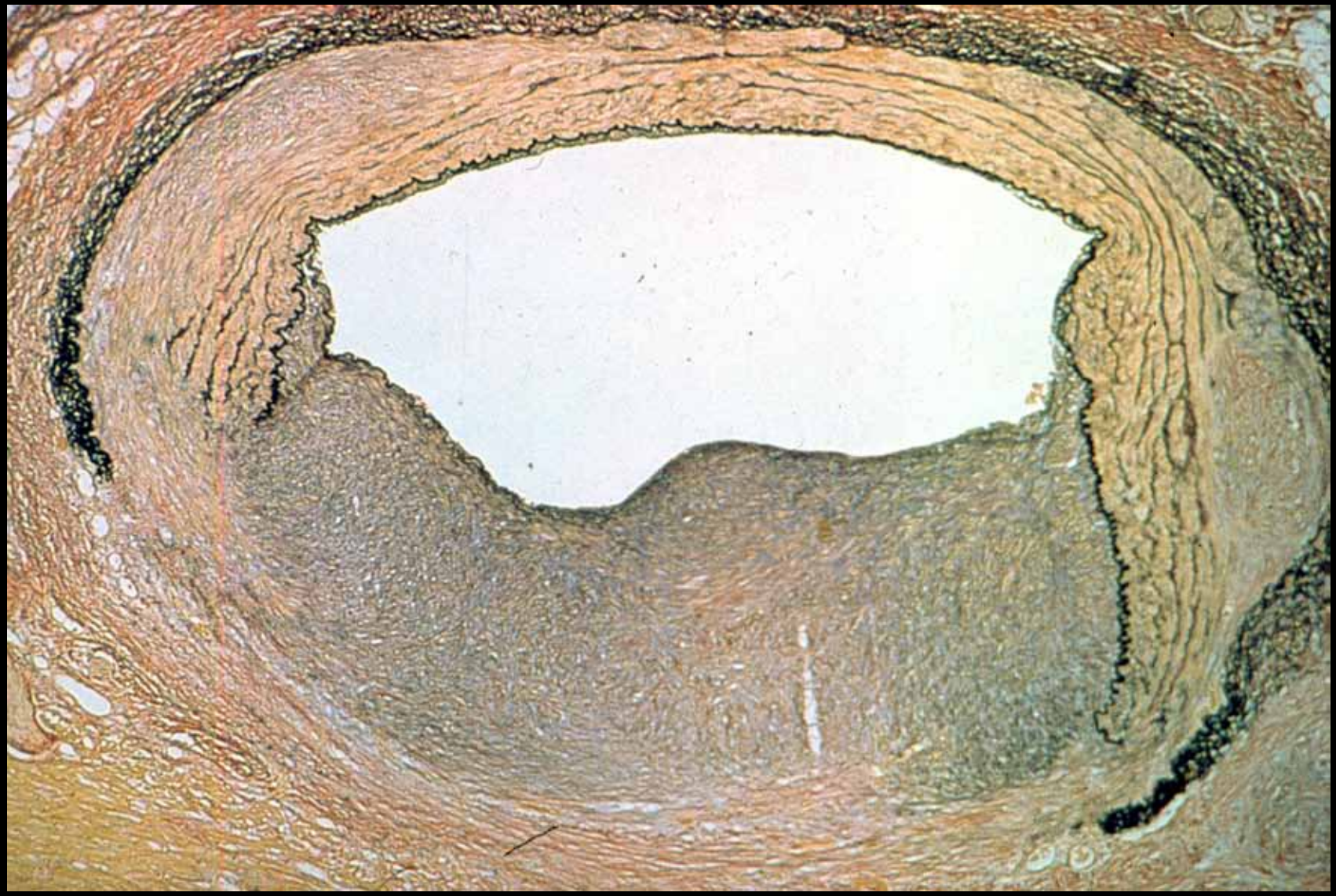



Balloon Angioplasty

Normal Artery



Restenosis Following Angioplasty

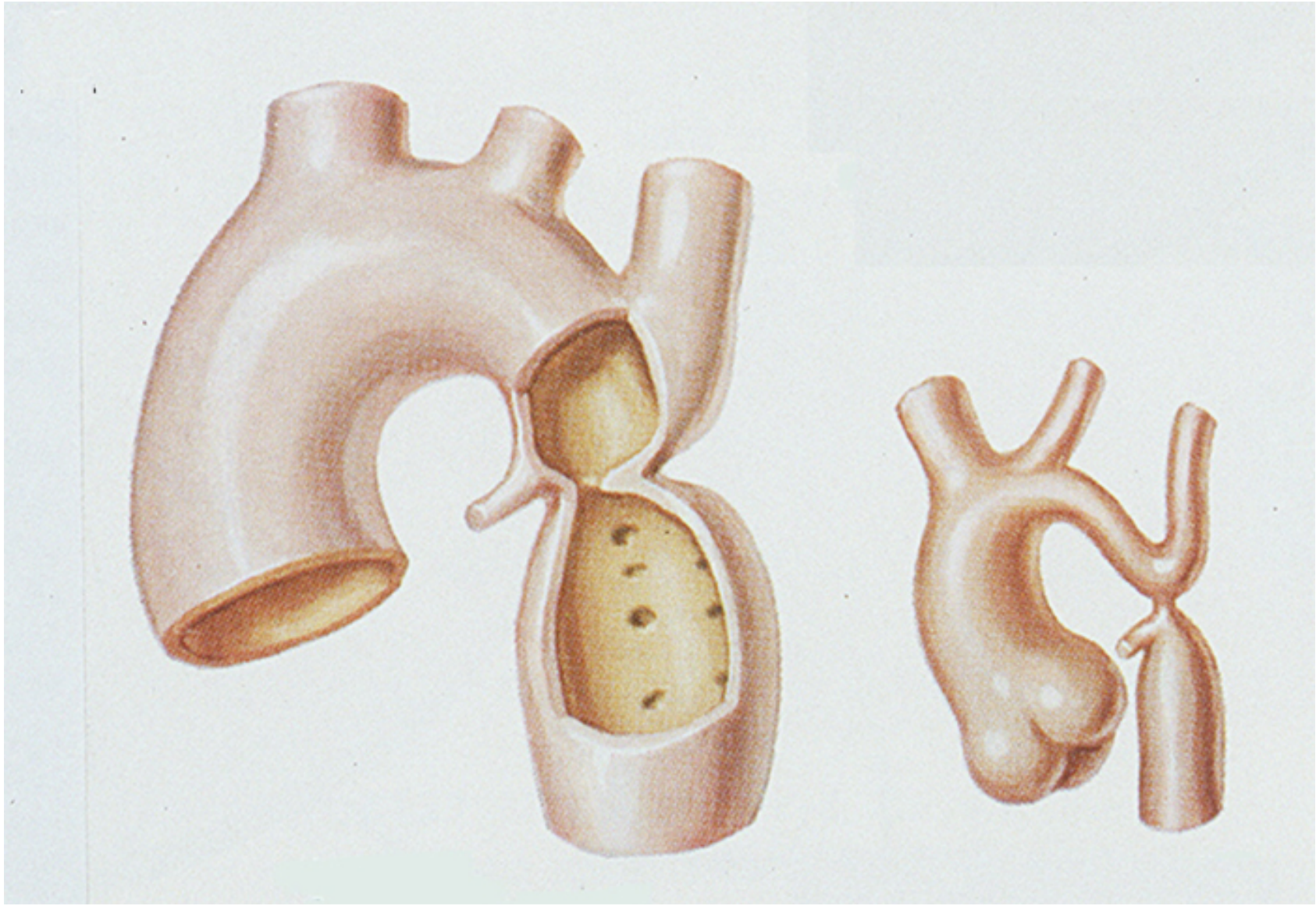


Porcine Neointima, 28 days after PTCA

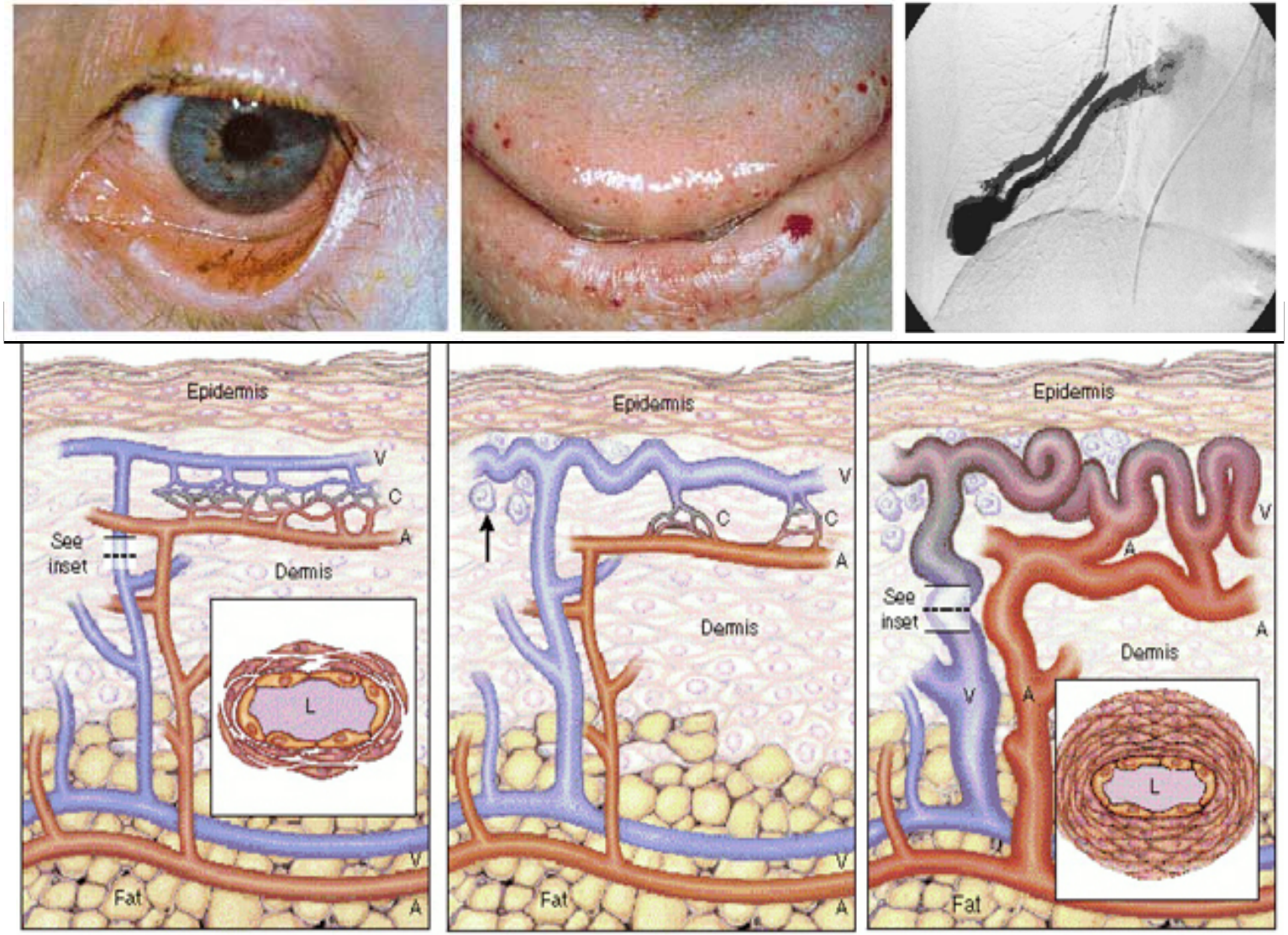
Congenital Vascular Defects

- Congenital cardiovascular defects are present in approximately 1/100 live births. Example- **Coarctation of the Aorta**
- Heart defects are often life-threatening and require early surgical intervention.
- Congenital vascular diseases can cause early defects or vascular defects later in life. Example- **Hereditary Hemorrhagic Telangiectasia**

Coarctation of the Aorta, a localized vascular occlusion of the aortic arch



Clinical Manifestations of Hereditary Hemorrhagic Telangiectasia: Telangiectasias and Arterial-Venous Malformations

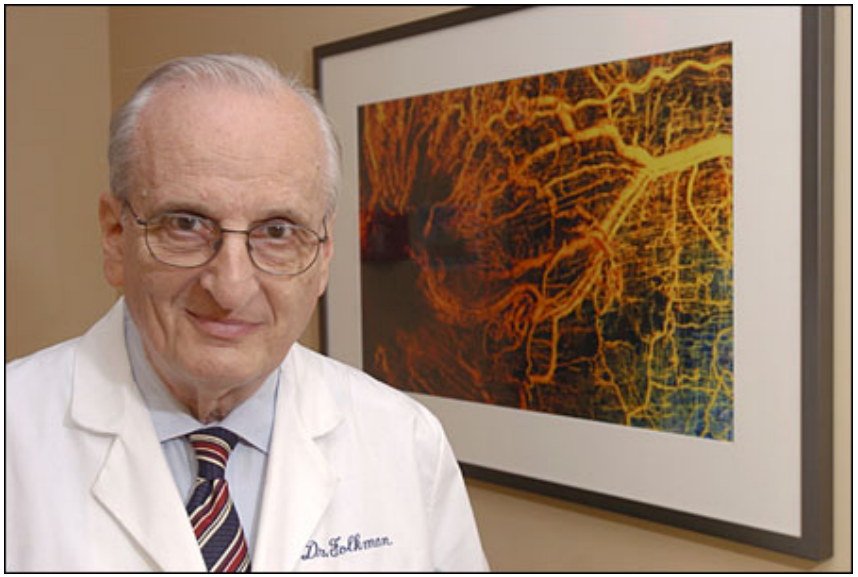


from Guttmacher et al. (1995). NEJM 333:918.

Blood & Lymphatic Vessels and Cancer

- Tumors stimulate the production of new host blood vessels to supply themselves with oxygen and nutrients.
- Antiangiogenic therapies can target newly these formed tumor blood vessels.
- Loss of a blood supply causes tumors to stop growing and regress.
- Lymphatic vessels are the major route for metastasis

Vascularization is essential for tumor growth and progression



Judah Folkman

Promoted from Instructor to Full Professor at Harvard in 1968

"The purpose of tenure is not financial security. The purpose is so that you can pursue a wild idea and not lose your job."

Antiangiogenic therapy for cancer